Review

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Review of current status of targeted alpha therapy in cancer treatment

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Abstract

Targeted alpha therapy is an emerging alternative for palliative therapy of a wide range of tumor types. Data from preclinical and clinical research demonstrates a high potential for the selective killing of tumor cells and minimal toxicity to surrounding healthy tissues. This article summarizes the developmental stages of alpha-targeted therapy from benchtop to commercialization. It discusses fundamental properties, production pathways, microdosimetry, and possible targeting vectors. Proper coverage has also been given to comparing it with other standard treatment procedures while exploring clinical applications of alpha emitters. In the end, like other therapies, the challenges it faces and its future impact on personalized medicine are also illustrated.

KEY words: targeted therapy; cancer; alpha particles; microdosimetry; targeting vectors

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Introduction

Cancer has been a dominant cause of death in the world characterized by the multiplication of cells in an uncontrolled fashion. Several treatments are available however, each technique has its benefits and limitations. The main challenge in a conventional way of cancer treatment is that most patients are unfit in the advanced stage [1]. Furthermore, chemotherapy is always associated with side effects in patients that jeopardize treatment compliance and therefore put emphasis to develop a new effective but less toxic therapy. One optimal solution is targeted therapy [2].

In contrast to external radiation therapy where the radiation source is at a distance from the patient, internal radiation therapy is performed by direct administration. Radiopharmaceutical, being a crucial component of internal radiation therapy, is a conjugate of biological molecules and radionuclides that target specific cells within the human body. Molecular radiotherapy (MRT) can offer distinct advantages over external beam radiation therapy (EBRT), with the right combination of labeling vectors effectively targeting cancerous tissue whilst minimizing the radiation dose delivered to healthy tissue. This can be particularly advantageous in the treatment of metastatic disease, where the use of large fields in EBRT can result in soft tissue toxicity and therefore is not always a viable option. For the therapeutic administration of radionuclides in MRT the red marrow, liver or kidneys are the common organs at risk that may exhibit toxicity and therefore can be a limiting factor in total activity administration to a patient [3].

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Therapeutic radiopharmaceuticals have seen exquisite development during the past two decades achieving high clinical throughput. Traditionally, there has been widespread use of beta-emitting radioisotopes for the treatment of various forms of cancers. However, particular radiation emitting from these radionuclides deposits a substantial amount of energy to regions outside the micro-metastatic tumor cells. For example, β particles from ^{90}Y deposit their energy (maximum energy 2.3 MeV) over a range of 12 mm. This distance is quite larger than the diameter of a single leukemia cell showing their inability to treat micrometastatic cancers [4]. Latest research and clinical trials proved the added benefits of alpha particles to bombard target cells of the micrometer range (path length $< 100\,\mu$m). The LET of α-particle is about 100 keV/μm, thereby, depositing excess energy in a unit length as compared to a β particle and other low LET radiations [5, 6]. This steep gradient in energy deposition makes alpha particles more cytotoxic for malignant cells with minimum harm to normal tissues. It is worth noting that only 15 alpha particles can deposit sufficient energy to the nucleus of the cell to cause programmed cell death (apoptosis) [4].

However, due to high-dose deposition, extensive dosimetric studies must be performed to evaluate the safety issues related to high cumulative doses in case of multiple cycles given to the same patient. The cytotoxicity of this high-dose deposition is largely dependent on the biodistribution of radioactivity in tissue samples that can be best studied in-vitro using alpha camera and time pix detectors. It should be noted that conventional ways of measuring average dose cannot be applied to doses deposited over submicron length by alpha particles. The concept of microdosimetry will be discussed later in this article to describe dose-measuring quantities developed specifically for dose distribution over short path length. Furthermore, to determine the biodistribution of radioactive atoms over the submicron region, researchers have developed the Cherenkov luminescence imaging (CLI) technique that uses optical light for the detection of charged particles through the medium and can be employed both in clinical and preclinical studies. The use of these detectors has been reported for the study of alpha particle biodistribution [7–10].

In 1914, radioiodine gained the distinction of being the first theranostic radiopharmaceutical for the therapy of thyroid disease [11]. Since then, the evolution of nuclear medicine from imaging to therapy beyond thyroid disorders is on the rise with great success. There are several review articles that summarize the current clinical experience with a particular radioisotope [12–15]. We, in this article, tried to present a summarized background to discuss the advances in knowledge of targeted alpha therapy (TAT), relevant dose estimation and implications for patient care in current practice, the potential advantage of TAT over other techniques, challenges and future prospects.

Targeting vectors

The cancer-specific ligands can be used as pharmaceutical carriers thereby allowing delivery to desired sites. Among the cancer-specific ligands, biological macromolecules (antibodies, antibodies fragments) nanocarriers/nanoconstructs, and small molecules (peptides and affibodies), each possesses advantages and pitfalls, were extensively studied under the domain of cancer theranostic.

Biological molecules

The therapeutic effectiveness of alpha radioimmunotherapy (RIT) is mainly determined by many factors including but not limited to the antigen target concentration, affinity of the antibody, vascularity of the tissues and antibody/antigen rate constants. However, it also depends on the innate characteristics of the energy of the emitting particles, their range in the tissue of interest and the magnitude of energy imparted. While large tumors can be treated with beta-RIT, alpha-RIT has the advantage of more focused targeting with the result of the killing of cancerous cells while sparing adjacent normal tissues due to a steep gradient in dose distribution [16–18].

However, in parallel with benefits, there are some challenges that should be addressed. Slow delivery and diffusion into tumor tissue result in excessive dose deposition to surrounding normal organs such as blood and liver. This issue can be solved by injecting antibodies to saturate the antigenic site before administering radioactive substances in normal organs. The development of smaller antibody fragments can be effective however these may cause unnecessary radiation to the kidney [19].

Nanocarriers

Nanoparticles and nanorods also provide unique properties for the diagnosis and treatment of cancerous cells. The ability to target specific sites, high loading capacity and longer retention time in tumors as compared to other radiopharmaceuticals make them potential candidates to kill abnormal cells inside the human body. However, the lack of discovery of suitable nanocarriers having favorable pharmacokinetics functionalities so far hinders their widespread use in a clinical setting. Some authors have devised ways to synthesize different nanocarriers with desired characteristics [20].

Small molecules

Contrary to conventional ways of treatment, cancer-specific peptides have several advantages over proteins and antibodies. Therapeutic peptides are smaller in size and therefore can penetrate the cell membrane. These have increased tumor selectivity, rapid synthesis, high activity and minimum drug resistance. Like other drugs, these peptides do not accumulate in the liver and kidneys, thereby, minimizing the toxic effects to these vital parts of the body. However, they also have some significant drawbacks. These peptides have a short biological half time and low stability, however, these problems have been overcome by the use of multiple antigen peptides (MAP) [21].

Alpha emitters

The physical characteristics, clinical significance and potential production pathway of some of the potential alpha particle emitters are discussed below (Tab. 1). The extremely short range of alpha particles makes it difficult to measure them *in vivo*. However, pharmacokinetic and dosimetric studies can be performed by accompanying gamma radiation. Furthermore, an alpha emitter with serial decay makes the situation more complicated due to the emission of daughter products having enough recoil energy to detach from the targeting vector. These recoil daughter product deposit energy away from their site of origin to normal tissues. The radioisotopes used for diagnosis and therapy purposes must show some desirable characteristics to make them eligible for widespread clinical use. First radioisotopes should decay by half-life neither too short nor too long. They should be readily available at an affordable cost. However, it has been observed that most alpha emitters do not meet these desirable characteristics and hence are restricted to limited use. Currently, alpha-emitters used for therapeutic application are ^{211}At, ^{225}Ac, ^{212}Bi, ^{213}Bi, ^{223}Ra, ^{224}Ra, ^{212}Pb, ^{226}Th and ^{227}Th [4, 12, 13]. Targeted alpha therapy (TAT) has been the subject of extensive research over the last two decades. Except ^{223}Ra with intrinsic targeting properties, most of clinical research has been conducted with generator-eluted radionuclide pair ^{225}Ac ($T_{1/2}$ = 9.9 d) and its short-lived daughter radionuclide ^{213}Bi ($T_{1/2}$ = 46 min) conjugated to a wide variety of vectors [14].

^{225}Ac/^{213}Bi

^{225}Ac decays to stable ^{209}Bi through 6 dominant daughters. An ^{225}Ac atom decays to produce 4 alpha-particles and 3 beta-disintegrations along with 2 isomeric gamma-emissions. ^{225}Ac is a therapeutically significant radionuclide when labeled with a suitable antibody. ^{225}Ac and ^{213}Bi are currently produced from ^{229}Th generator that is usually milked over a period of three weeks to separate ^{225}Ra and ^{225}Ac from each other. The production of large-scale and cost-effective cyclotron-based ^{225}Ac through the nuclear reaction ^{226}Ra (p, 2n) ^{225}Ac has been experimented nowadays [22].

Table 1. Useful characteristics of potential alpha emitter radioisotopes used in targeted alpha therapy (TAT)

Parent	Daughters radionuclide system	Half-life	α decay	Energy α [MeV]	Soft tissue range [μm]	Production	Emissions useful for imaging
^{211}At		7.2 h	42%	5.87	57	Cyclotron	77–92 keV X-rays
	/^{211}Po /^{207}Bi /^{207}Po	0.52 s/38 y/stable	100%	7.45			
^{225}Ac		10 d	100%	5.94	58	Generator ^{229}Th $\rightarrow$ ^{225}Ac	218 and 440 keV γ-ray
	/^{221}Fr/^{217}At/^{213}Bi	5 m/32 msec/45 min	100% (alpha by all isotopes)	6.45/7.2/5.87/8.38			
^{227}Th		18.7 d	100%	6.14	53	Generator ^{227}Ac $\rightarrow$ ^{227}Th	84, 95, 236 and 270 keV γ-ray
	^{223}Ra	11.4 d	100%	5.71			
^{224}Ra		3.63 d	100%	5.69	54		
	^{220}Rn/^{216}Po/^{212}Pb	55.6 s/0.15 s/10.6 h	100%/100%/--	6.29/6.78/---			
^{212}Bi		60.6 m	36%	6.05	71	Generator ^{224}Ra $\rightarrow$ ^{212}Bi	238 keV γ-ray
	^{213}Po/^{208}Tl/^{208}Pb	0.30 μs/3.1 m/Stable	100%/------	8.78/---			

^{213}Bi is a daughter product of ^{225}Ac. It has a half-life of 45.6 min. It decays to stable ^{209}Bi through the emission of one α particle and with an isomeric transition of 440 keV gamma radiation. It is eluted from ^{225}Ac/^{213}Bi generator thereby enabling its use in clinical centers. The drawback associated with this radionuclide is its short half-life and preferential accumulation of its daughter products in the kidney and urine [23].

^{227}Th/^{223}Ra

^{227}Th (Half-life = 18.7 days; energy of alpha particle = 6.0 MeV) and its daughter, ^{223}Ra (half-life = 11.4 days; energy of alpha particle = 5.7 MeV) are also called nanogenerator. It decays to stable ^{207}Pb by emitting four high-energy α-particles. ^{223}Ra decays sequentially to ^{219}Rn ($T_{\frac{1}{2}}$= 4 s), ^{215}Po ($T_{\frac{1}{2}}$= 1.8 ms) and ^{211}Pb by alpha-emission. ^{211}Pb ($T_{\frac{1}{2}}$= 36.1 min) decays into another alpha emitter ^{211}Bi ($T_{\frac{1}{2}}$= 2.1 min). The main source of production of ^{223}Ra for clinical uses is ^{227}Ac/^{227}Th generators. ^{223}Ra is an analog of calcium and accumulates in the bone. Gamma-ray spectroscopy of the femur revealed that ^{223}Ra caused an increase in radiation dose to the bone surface if released due to their recoil energy [24].

^{224}Ra/^{212}Bi

^{224}Ra, ^{212}Pb, and ^{212}Bi are daughter products of a long-lived parent, ^{228}Th. However, ^{224}Ra generators have replaced ^{228}Th based generators due to radiolytic damage occurring to resin. The generator is replaced after 1–2 weeks due to the short half-life of ^{224}Ra. ^{224}Ra ($T_{\frac{1}{2}}$= 3.6 days; energies of alpha particles 5.7-MeV with 241-keV gamma radiation) produces four alpha particles and two beta particles through its decay into stable ^{208}Pb. ^{212}Pb ($T_{\frac{1}{2}}$ = 10.6 hours; energy of $\beta-$particle = 93.5 keV) and ^{212}Bi ($T_{\frac{1}{2}}$ = 60.6 min; energies of alpha particles 6.1-MeV) are the main daughter products of this generator. Free ^{212}Pb distributes to the liver, kidneys, blood and bone while ^{212}Bi mainly grows in concentration in urine and kidneys [25].

^{211}At

^{211}At ($T_{\frac{1}{2}}$ = 7.2 hours) disintegrates into more stable radionuclide ^{207}Bi through alpha particle emission. Micro and nanodosimetry are not required in this case due to accompanying gamma radiation and therefore scintigraphy and conventional ways of measuring dose are sufficient. ^{211}At can be produced from irradiation of natural bismuth targets via the ^{209}Bi (α, 2n), however, low production poses hurdles in its widespread use, as it can only be generated at cyclotron capable of producing 28–29 MeV alpha particles. Now production via ^{209}Bi (Li-5,5n) ^{211}Rn reaction is envisaged. The biodistribution of free astatine in humans involves organs like the thyroid, stomach, spleen and lung [26].

Dosimetry

Dosimetry is a crucial step to evaluate the effectiveness of any radiation-based treatment. Since the goal of every treatment is to deliver maximum dose to tumor volume while sparing surrounding normal tissues. Radiation-induced toxicity to healthy tissues can best be estimated with the help of dose assessment techniques. So far, several ways have been devised to estimate the energy deposition that led to the development of more complicated methods with great accuracy.

Conventional dosimetric techniques do not provide accurate information when it comes to alpha particles. These dosimetric techniques do not consider factors like the geometry of the cells, their sensitivity to radiation and other biological factors while calculating absorbed dose. These factors contribute significantly in determining accurate energy deposition at a micro level. Therefore, microdosimetry or stochastic ways are more suitable to answer the unanswered questions regarding the dosimetry of alpha particles. Alpha particles are high LET radiation that delivers radiation to the biological medium in quite a different way. Alpha particles have short path lengths. That means they deliver all of their energy in a short linear track, however, in a non-uniform fashion.

They form a wide range of clusters of varying densities of ionization along their track. Due to these huge fluctuations of energy deposition, the concept of an average absorbed dose will no longer be applicable to characterize biological outcomes and the conventional ways of dose estimation fail to fully quantify the therapeutic efficacy of targeted alpha therapy [27].

Further because of high LET, the alpha particles deliver a dose to the volume of a submicron size that is even smaller than the size of the cellular dimension. The high deposition of radiation dose to the volume of cellular size makes alpha particles more cytotoxic. Another unique characteristic associated with alpha particle dosimetry is the non-uniform distribution of radioactivity in the tumor region due to the heterogeneous expression of the antigen. This heterogeneity in activity distribution leads to non-uniform energy deposition. Therefore, conventional ways of energy averaging to estimate the absorbed dose will fail under these situations and require other ways of dose determination on the submicron level. A concept of specific energy was introduced to deal with the micro-level absorbed dose and has the same units as that of conventional dose.

Furthermore, as more advanced physics models, realistic cell and DNA geometries and complex algorithms came into existence, specialized Monte Carlo simulation codes were developed to calculate absorbed dose more accurately to single or multiple cells on micro and nanoscale. These specialized codes are extensions of already developed general-purpose codes. Some examples of these specialized codes are Geant4-DNA and TOPAS-nBio etc.

As a first method, MIRD committee pamphlets 21 and 22 have been used for absorbed dose calculations for alpha emitters based on the concept of mean absorbed dose to the target volume. To improve MIRD formalism, a number of human body models have been developed to better approximate radiation interaction to the real situation inside the body. Later, 3D image-based voxelized phantoms of a variety of sizes and shapes were created to cope with challenges faced with new scientific developments. The voxel S method still uses a model-based approach for personalized dose assessment. In order to estimate the accurate spatial distribution of radioactivity, CT images are coupled with SPECT images where the former provides anatomical reference landmarks, however, the poor spatial resolution (5 to 25 mm) of functional imaging renders it difficult to incorporate the stochastic nature of alpha particle distribution that has a range of the order of 40–90 μm. To better resolve this situation, several groups made specialized alpha cameras called Ionizing-Radiation Quantum Imaging Detector that visualizes activity distribution in vitro on a micro level. Energy deposition points and absorbed dose on micro and nanoscale can be calculated using Monte Carlo methods. [17, 24].

Clinical trials of targeted alpha therapy

The most common forms of cancers are Prostate (6%), Pancreas (7%), Breast (7%), Colorectal (12%) and Lung (21%) [28]. Extensive research on targeted alpha therapy is being done around the globe either to cure or to increase the survival of cancer patients. In this section of the review article, we will go through developments made so far in clinical trials of alpha therapy. Alpha therapies, development phases and important findings in different clinical trials along with references are summarized in Table 2.

Neuroendocrine tumors

Neuroendocrine tumor (NET) begins in specialized types of cells that convert neuronal information into hormonal information. These nerve cells control a number of important physiological processes taking place in the body including but not limited to cellular metabolism, reproductive cell and degree of digestion. Treatment of neuroendocrine tumors varies according to their type and location but usually includes a combination of surgery, chemotherapy and radiotherapy [29]. However, radiolabeled somatostatin receptor (SSTR) agonists have proved superior to other modalities for the therapy of primary NETs and their metastatic lesions. DOTA-TOC, DOTA-NOC, and DOTA-TATE are tumor-targeting probes that mimic the endocrine-system regulating hormone somatostatin. The main difference among these three tracers is their variable affinity to SSTR subtypes. All of them can bind to SSTR2 and SSTR5, while only DOTA-NOC shows a good affinity for SSTR3.

Beta emitters with a higher affinity for somatostatin receptors have been successfully used in targeted radiotherapy but these have not shown promising results for hypoxia tumors. Radioisotopes emitting alpha particles are more toxic to tumors than those of beta-emitting particles as discussed before [30]. An alpha emitter ^{213}Bi or ^{225}Ac is attached with a nitrogen ring structure including a tetraazacyclododecane, a triazacyclononane, or a tetraazabicyclo[6.6.2]hexadecane derivative and somatostatin receptor have been extensively used. The first reported preclinical peptide receptor therapy was ^{213}Bi and ^{225}Ac labeled DOTATOC in a mouse. Further, the study of ^{213}Bi-DOTATATE in tumors of different sizes in mice demonstrated the great therapeutic effect for even larger neuroendocrine tumors [31]. The first in human investigation with ^{213}Bi labeled DOTATOC in 25 NET patients refractory to peptide receptor radiation therapy (PRRT) using beta ^{90}Y/[^{177}Lu]Lu-DOTATOC showed a long-lasting anti-tumor response [32]. To increase the dose to tumor cells instantaneously, it was injected intraarterial into the main tumor feeding vessel (max. dose of 20 GBq in five cycles). The results were found to be encouraging in targeting the tumor cells while sparing surrounding healthy cells. The study paved the way for subsequent investigations on patients diagnosed with advancing neuroendocrine tumors using ^{225}Ac-DOTATOC. The single-cycle means targeted dose was found to be 40 MBq while in multiple fractions two approaches may be adopted; either 25 MBq in every 4-month period or 18.5 MBq in a 2-month cycle [33]. Later, further research on new kinds of radiopharmaceuticals led to the development of DOTP tagged with ^{213}Bi which has higher efficiency than the previously used radiopharmaceuticals [34].

^{212}Pb-DOTAMTATE (AlphaMedix™), is currently being experimented with in patients diagnosed with metastatic SSRT-positive NETs. In phase 1 trial [35] safety and dose-limiting toxicity and pharmacokinetic properties are assessed by increasing doses of AlphaMedix$^{\text{TM}}$ in steps [36]. Subjects with no prior history of PRRT were selected during this trial. Efficacy assessment was done using [^{18}F]FDG PET/CT scans. Treatment was given in a single intravenous administration of increasing doses or multiple increasing doses consisting of three intravenous injections. Follow-up studies revealed few mild adverse cases (nausea and mild hair loss in 2 of 9 patients; abdominal pain and diarrhea in 3 of 9 patients, the fatigue in 2 of 9 patients). There was no dose-limiting toxicity [37].

Table 2. Targeted alpha therapy in clinical trials

Therapy	Indication	Activity (kBq/kg)	Development phase	Major end points/findings	Ref.
$^{223}\text{RaCl}_2$	Breast and prostate metastases	46, 93, 163, 213 or 250	I, 25 patients single center	Toxicity, mild transient diarrhea, nausea	29
	Prostate metastases	50/month for 4 months	II, 64 patients randomized	Irreversible neutropenia PSA progression	
		50 every 4 week × 6 doses	III, 921 patients randomized	Toxicity, ALP progression, symptomatic skeletal events, neutropenia, pain	
		5, 25, 50 or 100	II, 100 patients 25 per dose group, randomized	Nausea, fatigue, vomiting, diarrhea, constipation, bone pain, urinary tract infection and peripheral edema	
		25, 50 or 80 every 6-week × 3 doses	II, 122 patients randomized	Diarrhea, nausea anemia	
		50, 100 or 200	I, 10 single center	ALP and serum N-telopeptides	
$^{223}\text{RaCl}_2$ + enzalutamide	mCRPC	50/month for 6 months + 160 mg daily	III (PEAEC Trial) 560 patients randomized	Symptomatic skeletal event, pain progression	43
$^{223}\text{RaCl}_2$ + docetaxel		55 every 6 week × 5 doses + 60 mg/m^2 every 3 weeks for 10 doses	III (DORA trial) 738 patients randomized	ALP, PSA progression, osteoblastic bone deposition	
$^{223}\text{RaCl}_2$ + atezolizumab		55 every 4 week × 6 doses + 840 mg every two weeks	I, 45 patients randomized	Toxicity and grade ¾ adverse events. No clinical benefit was observed	
$^{223}\text{RaCl}_2$ + pembrolizumab		Every 4 weeks at a pre-determined dose + every 3 weeks at a pre-determined dose	II, 45 patients randomized	Recruiting, not yet reported	
$^{223}\text{RaCl}_2$ + sipuleucel-T		50/month for 6 months + 3 infusions each every second week after second dose of ^{223}Ra	II, 36 patients randomized		
$^{223}\text{RaCl}_2$ + niraparib (PARPi)		Every 4 week over 1 min. for 6 courses + daily	I, 14 patients single group		
$^{223}\text{RaCl}_2$ + olaparib (PARPi)		Every 4 week over 1 min. for 6 courses + PO BID on day 1–28	I/II, 120 patients randomized		
^{213}Bi-HuM-195mAb + cytarabine	Acute myeloid leukemia	1.04×10^4 to 3.7×10^4	I, 18 patients	Myelosuppression	14
		Cytarabine 200 mgm^{-2}/day for 5 days followed by ^{213}Bi-lintuzumab from 1.85×10^4 to 4.62×10^4	I/II, 31 patients	Thrombocytopenia, neutropenia, MTD 37 MBq/kg	
^{213}Bi-cDTPA-9.2.27mAb	Metastatic melanoma	1.85×10^6 to 16.6×10^6 kBq	I, 16 patients	Intralesional, adverse events not reported	
		5.5×10^4 to 94.7×10^4 kBq	I, 38 patients	Systemic, no adverse events	
^{213}Bi-DOTA-Substance P	Glioma	1.07×10^6 to 2×10^6 per cycle kBq	Pilot, 5 patients	Intratumoral injection, necrosis on MRI	
	Recurrent glioblastoma	2×10^6 (1–6 doses per 2 months) kBq	I, 18 patients	Epileptic seizures in 3 patients	
^{213}Bi-DOTATOC	GEP-NET	1–4 GBq in increasing activity × three doses	First inhuman, 7 patients	Intraarterial infusion, kidney toxicity and thrombocytopenia	
		$2.6–21 \times 10^6$ kBq every 2 months × 1–5 doses	I, 25 patients	Tumor feeding vessel or intravenous, moderate kidney toxicity	
^{213}Bi-[Thi^8,Met(O$_2$)^{11}]-substance P	Gliomas	14×10^6 kBq every 2 months × 8 doses	I, 61 patients	Implanted catheter system with subcutaneous port	
^{213}Bi-anti EGFR-mAb	Bladder cancer	$3.6–8.2 \times 10^3$ kBq	I, 12 patients	Intravesical instillation, complete remission in 3 patients	51

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Table 2. (cont.). Targeted alpha therapy in clinical trials

Therapy	Indication	Activity (kBq/kg)	Development phase	Major end points/findings	Ref.
^{225}Ac-DOTA-HuM195mAb	Acute myeloid leukemia	18.5 to 148 kBq	First in human, 18 patients	Myelosuppression, liver function abnormality MTD 3 μCi/kg	83
^{225}Ac-DOTA-HuM195mAb + cytarabine		Total administered activity 2.5 × 10^3 to 7.3 × 10^3 kBq	Phase I/II	Patients ≥ 60 yrs, neutropenia, bacteremia, pneumonia, cellulitis, transient increase in creatinine	
^{225}Ac-DOTAGA-Substance P	Glioma	1–6 cycles of 2 × 104 to –4 × 10^4 kBq in two months interval	I, 21 patients	Intracavitary/intertumoral injection edema, epileptic seizures, aphasia	71
^{225}Ac-DOTATATE	GEP-NET (SSTR positive)	100 every 2 months × 3 doses	I, 22 patients	Asthenia, abdominal pain, abdominal distension, weight loss, peripheral edema, headache, dizziness, and flushing	30
^{225}Ac-DOTATOC	GEP-NET	2.5 × 10^3 kBq every 4 months or 1.8 × 10^3 kBq every 2 months upto 7.5 × 10^3 kBq	I, 39 patients	Chronic kidney toxicity, MTD of sindle dose = 4000 kBq	92
^{225}Ac-PSMA-617	mCRPC	8 × 10^3 kBq with deescalating dose every 2-month × 3 doses	I, 17 patients	Xerostomia anemia requires modifications of the treatment regimen	92
		100 every 2 months × 3 doses	I, 40 patients		92
		8 × 10^3 kBq with deescalating dose every 2 month × cycles (range 1–8)	I, 73 patients		98
^{225}Ac-J591		13.3–93.3 single dose	I, 22 patients	Anemia, nausea, xerostomia and AST elevation	95
^{225}Ac-FPI-1434	Advanced refractory solid tumors	To be evaluated	First in human, 38 patients	Recruiting, not yet reported	99
^{211}At-ch81C6	Recurrent brain tumors	7.1 × 10^4 –3.5 × 10^5 kBq	First in human, 18 patients	Surgically created resection cavity (SCRC), aplastic anemia, seizures	74
^{211}At-MX35 F(ab')$_2$	Ovarian cancer	2.24 × 10^4 to 1.01 × 10^5 kBq/L	I, 9 patients	Intraperitoneal, retention in thyroid, no adverse events	55
		4.7 × 10^4 to 2.15 10^5 kBq/L	I, 12 patients	Urinary bladder, thyroid and kidney received (1.9, 1.8, and 1.7 mGy per MBq/L) doses	96
^{212}Pb-TCMC-Trastuzumab	HER-2 expressing malignancies	4 mg/kg trastuzumab followed by 7.4–2.11 × 10^4 kBqm^{-2}	First in human, 16 patients	Intraperitoneal, abdominal pain	12
^{212}Pb-DOTAMTATE	SSTR positive neuroendocrine tumors NETs	1.1 × 10^3, 1.5 × 10^3 and 1.9 × 10^3 three cycle dosing within 10 weeks	First in human, 50 patients	No significant acute toxicity	35
^{227}Th-3,2 HOPO-Anetumab	Advanced recurrent epithelioid mesothelioma or serous ovarian cancer	1.5 × 10^3 kBq and increase in steps of 1.0 or 1.5 × 10^3 kBq, with a antibody dose 10–50 mg	First in human, 228 patients	Recruiting, Not yet reported	56
^{227}Th-3,2 HOPO-Anetumab	Non-Hodgkin's lymphoma	1.5 × 10^3 kBq every 6-week × 4 doses	First in human, non-randomized, 21 patients	Recruiting, not yet reported	
^{227}Th-3,2 HOPO-PSMA	Metastatic castration resistant prostate cancer (mCRPC)	To be evaluated	First in human, non-randomized, 157 patients	Recruiting, not yet reported	

3,2 HOPO — 3,2-Hydroxypyridinone; ALP — alkaline phosphatase; DOTA — dodecane tetraacetic acid; DOTAGA — dodecane triacetic acid; DOTATATE — DOTA-Tyrosine3-octreotate; DOTATOC — DOTA-Tyrosine3-octreotate; DTPA — diethylenetriamine pentaacetate; EGFR — epidermal growth factor receptor; FPI-1434 — an insulin-like growth factor-1 receptor targeting humanized monoclonal antibody, a bifunctional chelate; GEP-NET — gastroenteropancreatic neuroendocrine tumors; mAb — monoclonal antibody; mCRPC — metastatic castration-resistant prostate cancer; MTD — maximum tolerable doses; PARPi — poly (ADP-ribose) polymerase inhibitor; poly (ADP-ribose) polymerase inhibitor; PSA — prostate-specific antigen; PSMA — prostate specific membrane antigen; TCMC — 2-(4-isothiocyanotobenzyl)-1, 4, 7, 10-tetraaza-1, 4, 7, 10-tetra-(2-carbamonyl methyl)-cyclododecane

Huge funding has been reserved by the research grant providers to support PET instrumentation development and synthesis of new TAT theranostic agents for the accurate detection and effective treatment of neuroendocrine tumors. In addition to alpha-emitting radiopharmaceuticals, attempts are being made to employ the same procedure for $\beta+$ emitting radioisotopes (^{89}Zr) for treatment planning and monitoring. Silica-coated nanoparticles have also been tested for this purpose however subject to challenges of stability issues. The theragnostic agent (^{225}Ac/^{89}Zr-octreotate silica nano-particles) is intended to be delivered using PRRT [30, 38].

Prostate cancer

Prostate cancer is most common in developed countries with a lifetime risk of about 1 in 6 men. In the post-prostate-specific antigen (PSA) screening era, in the majority of cases, radical proctectomy and radiation therapy are two main choices to treat the localized disease. However, androgen deprivation therapy is used to treat metastatic disease but mostly the patient goes into a castration-resistant state which is incurable with hormone and chemotherapy treatment [1, 39].

Bone metastases have been a target of recent research and various pharmaceuticals developed for the treatment of this cancer, only a few of them are FDA approved. Bone-targeted agents include Receptor activator of nuclear factor kappa-B ligand (RANKL), inhibitors (denosumab), bone-seeking radioisotopes [e.g. ^{89}Sr chloride and ethylenediaminetetramethylene phosphonate (EDTMP)-^{153}Sm] and bisphosphonates (zoledronate) have only pain palliative affect. These radiopharmaceuticals, however, failed to demonstrate an appreciable survival rate in clinical trials [40]. Attention has now been directed toward α-particle bone-seeking radionuclides such as ^{223}Ra. ^{223}Ra dichloride (Xofigo®) is the first FDA approved alpha particle emitting radioisotope synthesized for palliative therapy of bone metastatic castration-resistant prostate cancer. ^{223}Ra has a dual mode of action in the tumor environment. It reduces the tumor-induced abnormal bone formation and induces tumor cell death. ^{223}Ra has proved to increase overall survival (OS) alone or in combination with poly (ADP-ribose) polymerase inhibitor (PARPi). However, its weak chelation with biomolecules puts a limit on its widespread clinical use [41].

Prostate cancer cells highly express PSMA (prostate-specific membrane antigen) on their surfaces thereby enabling them for radioligand therapy [42]. Certain alpha emitters, for example, ^{225}Ac and ^{213}Bi conjugated to PSMA-617 or radioimmunotherapy with ^{227}Th conjugated to a monoclonal antibody (mAb) that bind to PSMA have been reported [14, 43].

However, to improve daughters' retention, nanoparticles for the treatment of prostate cancer have also been tested by a variety of research groups in preclinical studies. Small metal-phosphate nanoparticles formed by ^{225}Ac coprecipitated within PO_4 inside 100 nm polymersomes have been trialed. Synthesized ^{225}Ac-nanocarriers were injected in healthy mice intravenously in xenografted mice containing MDA-MB-231 well-vascularized tumors. High uptake of polymersomes in non-healthy tissues was noted [44]. Targeted liposomes loaded with alpha particle emitter ^{225}Ac were linked to A10 aptamers and J591 monoclonal antibodies that recognize the extracellular domain of prostate-specific membrane antigen protein. The range of the loading efficiency varies from 58–86 percent. Some studies revealed that both the radioactive J591 liposomes and J591 antibody show similar cytotoxicity. These radiobioconjugates were more cytotoxic than A10 aptamer-labeled liposomes [45]. Extensive research is going on to investigate the potential of these nanoparticles for clinical applications.

Bladder cancer

Bladder cancer is one of the most common types of cancer around the world. In the US only, it ranked 4th in men and 13th most common form of malignancies in women. The American Cancer Society reported that in 2017 a population of 79,030 developed bladder cancer while 16,870 people died of this disease in the United States only [46]. The incidence is more frequent in men than women and in elderly people [47]. Some researchers claim that about 75% of patients develop the nonmuscle-invasive disease (NMIBC) while 25% of patients show muscle-invasive disease (MIBC) [48].

Carcinoma *in situ* (CIS) invades neighboring tissue and therefore is considered a high-risk cancer type. Most of the patients suffering from CIS demonstrate overexpression of epidermal growth factor receptor (EGFR). Conventional ways of treatment include intravesical instillation of Bacillus Calmette-Guerin and transurethral resection, in conjunction with radical cystectomy. In a preclinical study on a mouse, a ^{213}Bi labeled anti-EGFR monoclonal antibody was used to treat intravesical therapy of CIS. The therapeutic response was monitored by bioluminescence imaging technique [49]. The study showed its therapeutic effectiveness and safety which were later confirmed in a follow-up study [50]. Based on the potential results on animal subjects, the study was later conducted on 12 patients which were already found resistant to standard treatments and planned for cystectomy. ^{213}Bi labeled anti-EGFR monoclonal antibody was injected into patients and the therapy was found safe without any deleterious effects. Out of 12 patients, tumor cells in 3 patients were completely eradicated while persistent tumor detection in the other 6 patients [51, 52]. These results paved the way for loco regional targeted alpha therapy of CIS with ^{213}Bi-anti-EGFR. It was observed that increasing the strength of administered dose and number of treatment fractions may lead to higher therapeutic efficacy, however, this is needed in detailed investigations [53].

Ovarian cancer

Ovarian cancer is a deadly gynecological malignancy among women. When initially diagnosed, about 70% of patients are at an advanced stage and the 5-year survival rate is less than 30% due to poor prognosis and high relapse rate. The transmembrane epidermal growth factor type II receptor (i.e., HER2) was found overexpressed in several human solid tumors for example ovarian, breast, endometrial, non-small cell lung cancer, prostate, colon and cervical cancer [54]. Chemotherapy, radiation therapy (EBRT) or non-specific inverse planning radiotherapy in conjunction with adjuvant therapies in the form of colloid preparations of ^{32}P or ^{198}Au have been the treatment of choice to enhance patient survival. However, normal tissue toxicity and relapse remain a matter of major concern. Various β-emitters, for example ^{131}I, ^{177}Lu, and ^{90}Y have been investigated in intraperitoneal radioimmunotherapy. Among them, therapy with ^{90}Y-HFMG (human milk fat globule-1, a mAb toward MUC-1) has proved unsuccessful and overall survival did not improve [26]. Consequently, additional therapy includes intraperitoneal TAT using specific mAb MX35 F(ab′)$_2$ fragments labeled ^{211}At in case of relapsed ovarian cancer after completing second-line chemotherapy could attain absorbed doses in submicron-sized tumor nodule safely [55]. Similarly, preclinical studies of ^{227}Th-trastuzumab for treatment of HER2 + positive ovarian cancer showed encouraging antitumor effects without serious toxicity, prolong survival and tumor growth delay [56, 57]. A clinical trial using an antibody covalently bound to ^{227}Th complexing hydroxypyridinone (HOPO) in a patient with serous ovarian cancer known to express Mesothelin is underway [58]. Nanocontructs are also being studied. Multivesicular liposomes linked to the monoclonal anti-HER-2 antibody have been investigated for the straight delivery of ^{225}Ac to tumor cells of ovaries. Enhanced binding efficiency of radiolabeled immunoliposomes to tumor cells of ovaries was demonstrated in some studies however the maximum efficiency of ^{225}Ac entrapment in multivesicular liposomes was not up to the mark and remains even less than 10% of total activity administered [4].

Melanoma

Melanoma is a skin cancer that develops pigment-producing cells called melanocytes with high metastatic potential. Melanoma ranked 9th in common malignancies with nearly 100 000 fresh cases registered every year only in the United States. When compared with other cancer types, the incidence of melanoma increased at a faster pace due to excessive sun exposure, especially in young Caucasian women [59]. For localized melanoma, surgery is the best choice and has a greater success rate however, for metastatic melanoma the survival rate becomes low. It has been observed that uveal melanoma (UV) or malignancy of adult eyes is less frequent than cutaneous melanoma. The mAb overexpressed in human melanoma is chondroitin sulfate proteoglycan (MCSP), also known as NG2. MCSP or NG2 has also been expressed on other tumors including glioblastomas chondrosarcomas and some leukemias. Ipilimumab (Yervoy®), pembrolizumab (Keytruda®) and nivolumab (Opdivo®) are worldwide-approved immune therapies for unresectable or metastatic melanoma [60]. Radiation therapies include Plaque brachytherapy, Stereotactic radiosurgery (SRS) with gamma knife and proton beam radiotherapy (PBT) [61]. For tumors where surgery is not a treatment of choice, intralesional TAT will be the best substitute and results in an increased survival rate. In preclinical and clinical trials, ^{213}Bi has been labeled to mAb 9.2.27 via bifunctional chelator DTPA. ^{213}Bi-AIC is hundreds of times more radiation toxic to melanoma cell line than a beta-emitting immunoconjugate [62]. TAT therapy has been proven useful by disrupting tumor-feeding vasculature. Additionally, TAT with longer-lived radioisotopes (for example ^{225}Ac and ^{227}Th) will result in larger and homogenous radiation doses to tumors as compared to radioisotopes having short half-lives (for example ^{213}Bi with a half-life of 46 minutes) [61].

Renal cell carcinoma

Carcinoma of renal cells is a lethal urological disease that primarily affects men in the 2:1 ratio worldwide. In the United States alone, renal cell carcinoma accounts for 74,000 new cases yearly. The primary therapy is nephrectomy but the metastatic disease is incurable by surgical removal. Systemic treatments using checkpoint inhibitors and Tyrosine kinase inhibitors (TKIs) were established however it provides responses in a small percentage of patients (7–8%) with toxicity and survival of 12 months only [63]. Stereotactic body radiotherapy (SBRT) has been a modality of choice to control intracranial renal cell carcinoma metastases, but for other organs, its effectiveness cannot be ensured due to limited data available [64].

^{131}I-labeled monoclonal antibody (G250) has been used for the treatment of renal cell carcinoma but lacks major responses [65]. Preclinical and clinical trials with CD70-targeting molecules including antibodies are being recently started due to the overexpression of CD70 in renal cell carcinoma. For the first time Hagemann et al. [66], conjugated Octadentate 3,2 hydroxypyridinone (3,2-HOPO) chelator to antibody CD-70 and labeled with ^{227}Th. The conjugate demonstrated major inhibition of the growth of tumors in the human renal cancer 786-O cell line-derived xenograft model. Similarly, the therapeutic efficacy of ^{225}Ac-DOTA-Girentuximab in mice bearing subcutaneous SK-RC-52 is underway [66, 67].

Breast carcinoma

Breast cancer is much more frequent in women around the world and is ranked second cause of death in women. A plethora of work has been carried out to devise a modality of treatment since conventional radiotherapy, chemotherapy and surgery have limitations in treating the disease of this organ. Toxicity, invasion of cancer cells to healthy tissues and genetic mutation of normal cells are some limiting factors that hamper the success of breast cancer treatment [68]. An alpha-emitting radioisotope, ^{223}Ra dichloride results in toxicity restricted in a local region in bone metastasis. Therefore, clinical trials, using ^{223}Ra dichloride, on human subjects with HER2 negative and hormone receptor-positive cancer have recently been started to investigate its therapeutic efficacy [69].

Breast cancer has an approximately a 20% risk of brain metastases. Preclinical trials of ^{225}Ac-DOTA-anti-PD-L1-BC conjugate showed promising findings in breast cancer treatment. However, programmed cell Death Ligand 1(PD-L1) forms a part of an immune checkpoint system preventing autoimmunity. ^{225}Ac-DOTA-anti-PD--L1-BC (3 mg/kg) tagged with 15 KBq radioactive atoms was administered in a mouse. A higher survival rate has been observed in these animals [7, 10]. Similarly, in preclinical studies, Anti-VCAM-1 antibodies labeled with ^{212}Pb (^{212}Pb-αVCAM-1) have successfully hindered the metastatic progression in patients with HER 2 positive disease with minimal damage to normal brain tissues. VCAM-1 is expressed in endothelial cells adjacent to early brain metastases [70].

Glioblastoma multiforme/brain tumor

Glioblastoma multiforme (GBM) is an aggressive form of tumor that starts in the cells of the brain. It has the worst prognoses among other various types of carcinomas causing 5260 deaths in 100,000 population per annum. Despite the use of standard therapies like surgery, chemotherapy and radiotherapy, the median survival ranges from 12 to 15 months. Current treatment strategies have focused on targets like transferrin receptor, mAb against tenascin-C, interleukin-4 and interleukin-13 receptors, neurokinin type-1 receptors to enhance survival rate [71]. Merlo et al. [72] used [^{90}Y/^{111}In-DOTA^{0}D-Phe^{1}Tyr^{3}]-octreotide against somatostatin type 2 receptor (SSTR2)-positive tumors however the incoherent expression of SSTR2 hampered the utility of the compound in glioblastoma [72].

Early-phase clinical trials with ^{131}I-labeled antibody tenascin-C indicated some incremental benefits if combined with conventional standard clinical procedures but normal brain cells are subject to extensive radiotoxicity from ^{131}I [73]. In contrast, less radionecrosis was reported with ^{211}At conjugated anti-tenascin-C 81C6 antibody thus presenting an opportunity to significantly improve molecular radiotherapy in current clinical applications [74]. The drug is administered into the resection cavity made after surgery. Similarly, antitumor effects and responses of PARP inhibitor (PARPi) with an alpha-emitter Astatine-211 [^{211}At] MM4 in a neuroblastoma xenograft model have been exploited. Poly (ADP-ribose) polymerase-1 (PARPi) is a DNA repair enzyme [75].

^{213}Bi labeled DOTA-Substance P (^{213}Bi-SP) was tested in a patient suffering from recurrent GBM [76, 77]. The neuropeptide Substance P labeled (SP), highly expressed in glioblastoma cells is the physiological ligand of the neurokinin-1 receptor. A relatively short half-life of ^{213}Bi poses the problem of less radioactivity distribution in relatively larger tumors. Instead, ^{225}Ac having a half-life of 9.9 days has been used. Doses of 20–40 MBq ^{225}Ac-DOTA-GA-SP were injected in patients and the results obtained showed a promising compound for the treatment of GBM [71]. In a recent study, 2–3 nm gold nanoparticles have been used to treat U87 glioblastoma cancer cells via a DOTA-derivative chelator (TADOTAGA) [78]. After a lapse of 22 days, the studies showed retardation in tumor size markedly thus signaling the therapeutic efficacy of using gold nanoparticles for the treatment of brain tumor cells.

Osteosarcoma

Osteosarcoma commonly metastasizes to the lung (more than 85%) and bone [79]. Multiagent chemotherapy and surgery are standard of care with a median survival of approximately one year. Samarium-based agent ^{153}Sm-EDTMP, a bone-seeking beta emitter, has been extensively studied for the palliative cure of bone metastases. Recently, radium dichloride (^{223}RaCl$_2$), with bone-targeting properties, has been approved for prostate cancer with bone metastases. This radiopharmaceutical has high efficacy and low radiotoxicity which are favorable properties for the treatment of osteosarcoma [80]. ^{223}Ra has been found to retain for a longer period in the liposome in human osteosarcoma compared to soft tissues. Liposomes have a spherical shape with a hydrophobic membrane that surrounds an aqueous solution. These dissolved hydrophilic solutes cannot readily pass through the bilayer membrane [4].

Hematological malignancies

Hematologic malignancies comprise about 9 percent of freshly diagnosed cancers and attack blood, bone marrow and lymph nodes. These include various types of leukemia: chronic lymphocytic leukemia (CLL), acute lymphocytic leukemia (ALL), chronic myeloid leukemia (CML), acute myeloid leukemia (AML), lymphoma (Hodgkin's and non-Hodgkin's (NHL) and myeloma. Chemotherapy is usually given but is associated with a high probability of remission. Cell transplantation (HCT) ensures long-term survival but depends on many factors like comorbidities, age and lack of an appropriate donor [81]. Beta emitters (^{131}I, ^{90}Y and ^{188}Re) labeled with a murine anti-CD33 mAb (M195) and its counterpart, lintuzumab, BC8, anti-CD66 mAbs have been used for AML before HCT but it induces nonspecific cytotoxic effects [82]. To overcome this problem, the first human clinical trial was performed with ^{212}Bi labeled to anti-leukemia antibody HuM195 [23]. For the more successful killing of tumor cells, trials using ^{213}Bi and ^{225}Ac labeled lintuzumab or Sequential Cytarabine and ^{213}Bi/^{225}Ac lintuzumab have been conducted on patients with refractory AML [83]. Direct conjugation of ^{225}Ac to lintuzumab using macrocyclic ligand 1,4,7,10-tetraazacyclododecane tetraacetic acid (DOTA) has been trialed [14]. Clinical trials based on ^{211}At-BC8-B10 in patients with high risk of ALL, AML and myelodysplastic syndrome treatment before stem cell transplant [84] and ^{223}Ra-dichloride with dexamethasone and bortezomib in multiple myeloma patients are already in progress [85].

Immuno-chemotherapy using alkylating agents and an anti-CD20 monoclonal antibody is a standard treatment scheme for non-Hodgkin's lymphoma and chronic lymphocytic leukemia. Therapies targeting CD37, a glycosylated transmembrane protein is another choice of treatment and can be used as an alternative to CD20 for B-cell malignancies. ^{90}Y-ibritumomab tiuxetan (Zevalin®) and ^{177}Lu-lilotomab satetraxetan (Betalutin®) are often used as targeting agents for low-grade relapsed B cell non-Hodgkin lymphoma and relapsed follicular lymphoma [12]. ^{212}Pb labeled IgG1 chimeric antibody NNV003 and chelator TCMC (^{212}Pb-NNV003) has successfully been tested in a mouse model. NNV003 binds with high affinity to CD37 [86]. Encouraging findings in 20 percent of cases have been noticed with ^{213}Bi-CHX-A″-anti-CD20 radioconjugate with radiation doses up to 1640 MBq in patients with non-Hodgkin lymphoma disease. A BAY1862864, an anti-CD22 antibody conjugated to ^{227}Th, is the subject of extensive research in patients with refractory/relapsed CD22-positive non-Hodgkin lymphoma [12, 87].

After successful experimentation of carbon nanotubes in other fields of science, their potential use in TAT was first reported in 2010. Single-wall carbon nanotubes (SWCNT) were used as carriers for ^{225}Ac. The external wall of SWCNTs having dimensions of 350 nm in length and 1.2 nm diameter with primary amines was replaced with DOTA, a bifunctional chelator, linked to a morpholino oligonucleotide complementary to a functionalized antibody (cMORF) and in the last conjugated with ^{225}Ac. The preclinical studies in mice showed that multistep therapy, using mAb-MORF proceeded by SWNT-cMORF-(^{225}Ac) DOTA, have been extremely successful in eliminating lymphoma tumors [88].

Lung cancer

Lung cancer accounts for an estimated 154,050 deaths in 2018 worldwide and is one of the major cause of death from cancer in men [89]. Non-small cell lung cancer was common in 85% of lung cancer patients while the remaining 15% had small cell lung cancer. Unfortunately, targeted therapy, in this case, has not been successful and only a small fraction of patients got benefitted from this choice of treatment.

Woodwerd and coworkers studied La(^{225}Ac)PO$_4$ nanoparticles (NPs) conjugated to a monoclonal antibody (mAb 201B) and showed that these were expressed in lung endothelium. Furthermore, micro SPECT/CT was done to visualize biodistribution of La(^{225}Ac)PO$_4$ NPs-mAb that revealed uptake in the lung region post intravenous injection. It was demonstrated, in another study, that about half of the recoil daughter radionuclide was retained in the target area after 1 hour of post-injection. In order to lengthen the retention time, ^{225}Ac was loaded in the {La0.5Gd0.5}PO$_4$ core [90, 91].

Challenges and future propectus

Currently, targeted alpha therapy is a novel therapeutic modality that has the ability of localized cell killing mainly due to excessive energy deposition over small distances. This is due to two main characteristics: high linear energy transfer (LET) and short-range penetration[92].

However, in spite of promising characteristics necessary for the killing of abnormal cells, targeted therapy using alpha particles, like other therapies, also faces many challenges like lack of appropriate ligands, safety issues and availability in achieving desired goals. There are several ways to address these challenges, for example, by conjugating alpha particle emitters to specific biological molecules that have the capability of permeating the cell membrane thus ensuring a continuous supply of alpha emitters. Recoiling daughter nuclides may leave the target site that may deposit excessive energy to normal surrounding tissues and damage them. To cope with this situation, researchers have adopted many strategies including the encapsulation of alpha-particles in nanocarriers or the development of multivalent forms that have the capacity to internalize swiftly into target cells [12]. A smart drug delivery system is another way of transporting these compounds to the target site to achieve desired therapeutic effects. These systems have desired properties including tumor targeting ability, bio-compatibility, decreasing of side-effects, nonspecific distribution and accumulation. In this way, the main problem of undue radiation exposure to healthy tissues by the free daughter radionuclides can be removed significantly [92]. Promising results have been obtained in terms of safety and efficacy when seeds of low activity of ^{224}Ra were inserted surgically in some solid tumors of the head and neck [29].

Alpha-emitting drugs can be administered by intralesional, orthotopic or systemic injection. Dosimetry plays a pivotal role in optimizing and personalizing a therapy. Efficacy of alpha therapy has been established to metastatic melanoma, leukemia and GBM well below the maximum tolerable doses (MTD). However, further investigation is required to standardize the radiation doses. Frequently used the MTD are 1mCi per kg with ^{213}Bi-AIC for acute AML and about 0.14 mCi per kg for intra-cavity therapy of GBM in conjunction with ^{211}At-IC. For a few melanomas, MTD dose is even less than 0.3 mCi per kg although for metastatic lesions, these doses have not been established yet [29].

An accurate trade-off between tumor uptake and clearance is essential. Neither rapid nor slow radionuclide clearance from tumor cells brings the expected results. Fast clearance results in insufficient organ irradiation for a sufficiently long time causing an inadequate adsorbed dose to target cells. However, too slow clearance will cause toxicity due to the longer stay of radioisotope in cells. Therefore, strategies have been developed to solve these challenges. Currently, ^{211}At and ^{213}Bi have emerged as the most favorable and result-oriented alpha-emitters candidates due to desirable properties for example easy availability and daughter products. A pre-targeting strategy has been adopted in cases when the half-life of these radionuclides is short to put a limit on the required retention time. These pre-targeting strategies help enhance the therapeutic index thereby eliminating the issue of the short half-life of alpha particle emitters [19].

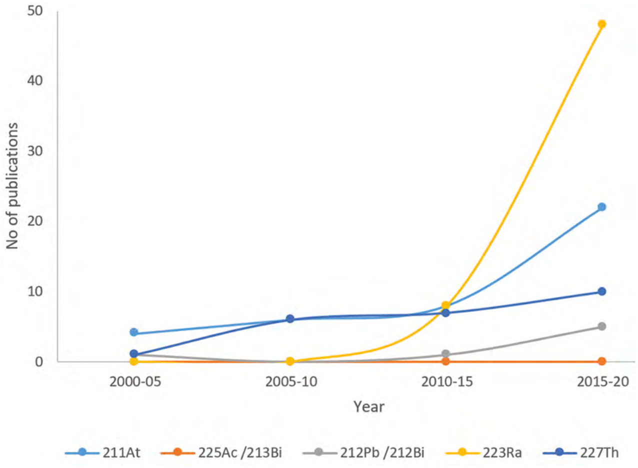

Figure 1. Publications per year related to targeted alpha therapy

TAT could potentially change the treatment paradigm in several cancer indications. ^{225}Ac and ^{213}Bi have been successfully utilized in alpha immunotherapy but ^{213}Bi is the major impediment due to the induction of renal toxicity. There are also other factors that should be carefully considered to make TAT an effective tool in tumor management. Some of these factors are level of antigenic expression on abnormal cells, specificity of the antibody/targeting construct, the existence of diffusion barriers, a quantity of unlabeled anti-body/targeting, selection of radionuclide, low specific radioactivity etc. [26]. Tumor heterogeneity and limitation on the low number of biological receptors can be dealt with by installing artificial receptors [93].

Despite these challenges, alpha therapy is making progress from promising preclinical findings to clinical trials. Xofigo® (Alpharadon, Radium-223 chloride) is the sole approved drug in the US for clinical use in mCRPC. Micro and nano-meter scale dosimetric approaches are now being explored to calculate accurate radiation doses from alpha-emitters employed in targeted therapies. Controlled and randomized clinical trials on a substantial number of patients to enable adequate comparison and as a result investigation of various treatment strategies is needed to conduct [26]. The major issue that hampers the broad use of alpha emitters is large-scale production as well as affordable cost [94].

Despite uncertainties and hurdles, prolonged survival and dramatic improvement in life have reinforced interest in theranostic nuclear oncology commercially [95]. Figure 1 shows the use of different alpha-emitting radionuclides over time for internal radiotherapy as listed in the PubMed database (based on preclinical and clinical research). There has been a tremendous increase in alpha trials after the FDA approval of Xofigo (radium dichloride) in 2013. Publications per year related to targeted alpha therapy demonstrate a six-fold increase in the last 10 years with a high prevalence of ^{223}Ra and ^{211}At studies [96]. However, in 2020–2021 with the global spread of COVID-19, research activities are more diverted toward developing potential uses of radiopharmaceuticals in antiviral treatment.

Recent developments in the alpha camera make *ex vivo* imaging of alpha-particle deposits at a cellular level a reality. A further emerging strategy is to pair short-lived alpha-particle emitters with rapid and specific targeting nanobodies. Recently ^{134}Ce (positron emitter) as a pair analog to ^{227}Th and ^{225}Ac represents an excellent therapeutic candidate in several cancers types by imaging the location of alpha emitters inside the body [97]. Recently positive response rates and overall survival of mCRPC treated with ^{227}Ac-PSMA-617 have been published [98]. First in human clinical study to investigate the anti-tumor activity of ^{225}Ac-FPI-1434 (an insulin-like growth factor-1 receptor targeting humanized monoclonal antibody, a bifunctional chelate) in patients with solid tumors is also envisaged [99].

However, for future development, adequate research funding, thorough training and vast methodological, interdisciplinary competence is a must to bring clinical findings of any significance to patients.

Conclusions

Alpha particle has been proven as an emerging internal radiation therapy source. It is highly cytotoxic yet their effect is extremely focused compared to therapies use beta particles. Although targeted alpha therapy is in the development stage it gives hope of life for cancer patients who is refractory to other modalities. Imaging with a suitable radiolabeled vector, dosimetry, management planning, and combination therapy are crucial parts of personalized treatment. To the best of our knowledge, we expect two important developments in TAT in near future. First the use of a carrier that restricts the release of recoil daughter products to normal tissues. Second, synthesis of a carrier that provides controlled release of alpha particle emitters in series through diffusion. Attention may be given to cheap production pathways of radioisotopes, infrastructure, in-depth training in the field of radiopharmaceuticals sciences and oncological nuclear medicine and multidisciplinary endeavor to get full scope spectrum in the global market.

Conflict of interest

The authors have no conflicts of interest to declare.

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