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Molecular Targeted α -Particle Therapy for Oncologic Applications

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Abstract

OBJECTIVE—A significant challenge facing traditional cancer therapies is their propensity to significantly harm normal tissue. The recent clinical success of targeting therapies by attaching them to antibodies that are specific to tumor-restricted biomarkers marks a new era of cancer treatments.

CONCLUSION—In this article, we highlight the recent developments in α -particle therapy that have enabled investigators to exploit this highly potent form of therapy by targeting tumor-restricted molecular biomarkers.

Keywords

²²⁵Ac; ²¹³Bi; ²²³Ra; α -particle therapy; molecular radiotherapy; nuclear medicine; radioimmunotherapy

For the past half century, investigators have been trying to specifically target malignancy with highly potent payloads that do not harm normal tissue. Although achieving this goal remains elusive, recent separate developments in molecular biology and nuclear medicine have shown the feasibility of this approach in clinical trials. These advances include the recent U.S. Food and Drug Administration (FDA) approvals of an α -particle therapy against prostate cancer [1] and a separate drug antibody conjugate against breast cancer that targets the *HER2/ERBB2* (formerly *HER2/neu*) biomarker [2]. New methods that combine these two innovations into a single targeted therapeutic strategy promise to approach the elusive goal of creating a “magic-bullet” therapy that will specifically target and eradicate cancer cells without harming normal tissue.

Molecular Delivery Platforms

Advances in molecular biology have uncovered a large number of tumor-restricted biomarkers that are expressed in high quantity in malignancy. These biomarkers, in

combination with the ability to produce monoclonal antibodies against practically any molecular entity, have led to the development of a myriad of specific antibodies, each with the potential to bind to a defined molecular target. However, for an antibody to have translational potential, it requires a number of characteristics, including a very high affinity to the intended target, the ability to bind a properly folded target biomarker, and the ability to bind to an area on the target biomarker that is accessible to circulating therapeutics, usually on the extracellular portion of the cell. Because numerous antibodies have been produced that contain these attributes, it has become obvious that additional criteria are needed to develop a safe and efficient way to target therapeutics.

First, many of the early antibodies were of mouse origin, which elicited a potentially fatal human antimurine antibody (HAMA) immune reaction that had the potential to cause significant morbidity [3, 4]. Although only a small minority of patients may have experienced such reactions, even a small number of serious adverse events can derail a diagnostic or therapeutic agent, as was shown by the withdrawal of the murine antibody ^{99m}Tc -fanolesomab from the market after a small number of unexplained fatalities [5, 6]. The limitation of HAMA reactions has since been overcome by the development of humanized antibodies that replaced much of the mouse portion of an antibody with its human analog, significantly limiting the issue of HAMA reactions [7].

Although this technique led to a new generation of antibody-based therapeutics that involve injecting naked antibodies against various disease modulators, these therapies remain limited to exceptional cases where the antibody itself modulates a biologic response when binding to its intended receptor. For example, rituximab is an antibody against the CD20 biomarker that is clinically approved for CD20-expressing lymphomas. It was originally developed as a mouse anti-CD20 antibody but was modified into a chimeric antibody that contains the human gamma-1 heavy chain and kappa light chain constant regions to limit the HAMA response and improve targeting. Rituximab is clinically effective by itself because it triggers apoptosis in CD20-positive lymphocytes via a number of mechanisms, including rituximab-mediated cell signaling, antibody-dependent cellular cytotoxicity, and complement-dependent cytotoxicity.

Although antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity are intrinsic characteristics of many antibodies, these mechanisms alone have proven to be inefficient at killing solid tumors in the absence of additional contributors. This has limited therapeutics largely to antibody biomarkers that have effector functions, which are mediated by antibody docking. For example, *HER2/ERBB2* is a biomarker found in approximately 30% of the tumors of patients with breast cancer [8]. These tumors can be targeted by trastuzumab, a humanized FDA-approved antibody for treatment of *HER2/ERBB2*-expressing tumors [9]. On engagement, trastuzumab prevents *HER2/ERBB2* dimerization, which is a critical step for downstream activation of *Akt* phosphorylation and tyrosine kinase Src signaling, leading to cell-cycle arrest. Thus, trastuzumab directly mediates downstream signaling that results in cell death [9]. Although there has been modest success treating patients with unconjugated trastuzumab, the development of resistance has prompted the development of improved anti-*HER2/ERBB2*-targeted therapies [10].

One such advance was to attach potent chemotherapeutics directly to the antibody and thus target the payload only to cells that express *HER2/ERBB2* (Fig. 1). This innovative strategy has led to the recent FDA approval of trastuzumab emtansine, which is composed of trastuzumab stably conjugated to the chemotherapeutic mertansine (also known as DM1) [2]. Although mertansine alone causes the expected severe adverse effects of a chemotherapeutic agent, conjugating it to tumor-targeting antibodies results in a significantly higher intratumoral concentration compared with normal tissue and thus dramatically increases the therapeutic window [11]. In the phase 3 EMILIA (Trastuzumab Emtansine [T-DM1] vs Capecitabine + Lapatinib in Patients With *HER2*-Positive Locally Advanced or Metastatic Breast Cancer) clinical trial that led to the FDA's approval of trastuzumab emtansine, there was a remarkable 6-month survival improvement in patients with *HER2/ERBB2*-positive locally advanced breast cancer receiving trastuzumab emtansine [11]. This led to the first approval of an antibody-drug conjugate in any solid cancer and has spawned the development of many additional such agents that promise to revolutionize cancer therapy.

Although antibody-drug conjugates are a significant advance in the field of molecular targeted therapy, there are a number of shortcomings that may limit their ability to completely eradicate tumors. First, cancer-restricted biomarkers are heterogeneously expressed within a tumor, leading to a clonal selection of cancer cells that no longer express the targeted biomarker or develop mutations that no longer permit the targeting agent to bind [12, 13]. This change in expression results in cells that are no longer killed by the antibody-drug conjugate. Second, cancer cells have the ability to become resistant to the chemotherapy payloads via a number of proven mechanisms, leading to a clonal selection of cancer cells that can evade chemotherapies [14]. Therefore, many strategies have emerged to prevent cancers from developing resistance to biomarker-targeted therapies, including targeting more than one cancer-restricted biomarker or using multiple chemotherapies with diverse mechanisms of action. One very promising strategy to overcome this resistance is to target potent radioactive isotopes specifically to tumors via molecular delivery systems such as antibodies and derivatives.

The Evolution of Targeted Nuclear Molecular Therapy

For over 50 years, nuclear medicine physicians and investigators have been pursuing the vision of molecular targeted nuclear therapy. This enthusiasm likely results from the successful use of ^{131}I in patients with differentiated thyroid cancer. Because only normal thyroid and differentiated papillary cancers express the sodium iodide symporter, only these cells take up the radioactive iodine and are efficiently eradicated by systemic administration of ^{131}I . Excitement for using molecular targeted radiation was further reinforced by the increased survival in patients with lymphoma treated with radiolabeled anti-CD20 antibodies ^{90}Zr -ibritumomab tiuxetan or ^{131}I -tositumomab [15, 16]. However, toxicities and perceived complexities of the anti-CD20 therapies have limited these therapies from reaching critical mass despite their proven benefits [17]. Furthermore, the lack of overwhelming responses in a number of trials using radiolabeled antibodies in large solid tumors has dampened some enthusiasm for this approach. However, the lessons learned from these first-generation agents have led to significant advances in molecular biology and

new approaches of targeting tumors with radioisotopes that include redesigned delivery systems and strategies that incorporate highly potent and specific α -particle emitters.

Redesigning the Delivery System

Antibodies were thought to be ideal for molecular targeted nuclear therapies because of their high affinity for tumor-associated biomarkers. However, their large size prevents them from rapidly clearing the blood pool (Fig. 2A). This characteristic leads to a large dose of radioactivity being administered to hematopoietic cells and results in dose-limiting neutropenia that has stymied the efficacy of early clinical trials that used whole antibodies to deliver therapeutic radionuclides to cancer. To address this issue, investigators have taken a number of approaches. First, many groups have found that reducing the size of an antibody by removing large parts of the constant region facilitates rapid clearance and increases tumor-to-blood ratios [18, 19]. For example, engineered antibody fragments developed by Kenanova et al. [20] against the carcinoembryonic antigen showed significant blood clearance and tumor-to-background targeting compared with the whole antibody. An additional approach has been to use peptides against tumor-restricted biomarkers. Given their small molecular size compared with antibodies, peptides have shown significantly better tumor-to-blood ratios compared with whole antibodies (Fig. 2B). A number of clinical trials using radiolabeled somatostatin analogs against neuroendocrine malignancies are showing the promise of this approach. Although peptide-based approaches have shown favorable results compared with the other limited therapeutic options, methods of kidney protection must be instituted because of the affinity of peptides for the renal parenchyma (Fig. 2B). Other promising targeting techniques that seek to overcome the toxicities associated with whole antibodies and peptides include radiolabeled peptidomimetics [21], affibodies [22], and dendrimers [23]. The increased excretion of these lower molecular weight agents limits the radiation dose to normal tissue and improves tumor penetration compared with whole antibodies.

Rethinking the Nuclear Payload

Traditional nuclear medicine strategies that deliver therapeutic radioisotopes to tumors rely on β -particle-emitters such as ^{131}I , ^{67}Cu , ^{177}Lu , and ^{90}Y . Linear energy transfer (LET) describes the density of ionization produced in the radioactive emission path. Beta-emitting radioisotopes are classified as low LET and kill cells indirectly, primarily by ionizing reactive oxygen species that cause single-stranded DNA damage. Furthermore, β -particle-emitters have a long spatial path (millimeter range), which exposes large amounts of surrounding tissue to its damaging effects. This long range of action can be beneficial in terms of a cross-fire effect, where tumor cells that do not express the targeted antigen also get exposed to the radiotherapeutic. However, it is also the cause for some toxicities observed in therapeutic strategies that use delivery systems that have long blood-pool half-life periods, such as antibodies. Furthermore, an additional shortcoming of these low-LET β -particle-emitters is that a lot of molecules need to get to a tumor to kill it, especially when treating solid malignancies. This deficiency is exacerbated by a tumor's ability to upregulate repair mechanisms and develop radioresistance, requiring an even higher and possibly unattainable dose of therapy. These shortcomings of β -particle-emitter-based nuclear

therapies are likely the reason for the suboptimal performance of these agents in clinical trials, especially in strategies that used high-molecular-weight antibodies.

The Promise of α -Particle Therapy

Alpha-particles are higher weight particulate emissions that are ejected from the nucleus of specific radioactive isotopes and can elicit catastrophic damage to cells in their path. Unlike β -particles, they travel a short linear distance (a few cell diameters) from the decaying nucleus and deposit a very large amount of energy in the path they travel [24]. This high LET is responsible for their enhanced cell-killing efficiency at concentrations far below those needed to achieve the same cell-killing efficiency of low-LET β -particle-emitters. Furthermore, the high LET that occurs within the cell nucleus elicits irreparable double-stranded DNA breaks, which result in the activation of numerous cellular pathways, including autophagy, necrosis, and cell-cycle arrest.

It is estimated that as few as one to three α -particles passing through the nucleus can cause irreparable DNA damage and inevitable cell death [25], making α -particle-emitters 100- to 500-fold more potent than low-LET β -particle-emitters. Importantly, α -particles do not rely on the generation of indirect reactive oxygen species, leaving their potency undiminished by tumor hypoxia, which is a cause of radioresistance to low-LET radiotherapies such as β -particle-emitters [26]. Furthermore, the potency associated with their high LET has been found to overcome the chemoresistance that commonly develops after traditional chemotherapy. Therefore, the high LET and precision of α -particle therapy is similar to the cytotoxic profile of proton-beam radiotherapy [27] but has the advantage of being potentially coupled with molecular delivery systems that can target small nests of infiltrating or metastatic cancer cells located in predominantly normal tissue. In this paradigm, α -emitting radioisotopes are conjugated to tumor biomarker targeted scaffoldings that bind to and eradicate tumor cells only, not normal tissue.

A number of groups have shown the power of molecular targeted α -particle therapy in various preclinical and clinical settings. For example, Wild et al. [28] directly compared the efficacy and toxicity of a bombesin peptide radiolabeled with either an α -particle-emitter (^{213}Bi) or a β -particle-emitter (^{177}Lu) in a preclinical mouse xenograph model of prostate cancer. They reported that the α -particle therapy had a 100% response rate (70% complete and 30% partial), compared with a 30% response rate (20% complete and 10% partial) for β -particle-emitter therapy, showing the power of using high-LET molecular targeted therapy [28]. Furthermore, α -particle therapy has been used in a number of clinical trials and has shown promising therapeutic potential [29–35] (Table 1). For example, investigators first used an ^{131}I -labeled antibody that targeted tenascin-C, an extracellular matrix glycoprotein that is overexpressed in glioblastoma multiforme [32]. Although early phase clinical trials indicated some incremental benefit of ^{131}I -labeled mouse antibody in combination with standard clinical care, extensive radiotoxicity occurred to the normal brain tissue from ^{131}I . In contrast, when ^{211}As was conjugated to the antitenascin-C 81C6 antibody, there was less radionecrosis compared with patients treated with ^{131}I -81C6, likely secondary to the much shorter path of α -emissions. This and other clinical studies in different malignancies confirm that the strength and short distance traveled by high-LET α -particles make them more

suitable than β -particle-emitters for some molecular radiotherapy applications [36–39]. Thus, innovative strategies that exploit molecular targeted high-LET nuclear-based therapies against tumor-restricted biomarkers present an opportunity to significantly improve on the current clinical agents.

A Milestone for Targeted α -Particle Therapy

In 2013, the FDA approved ^{223}Ra dichloride for clinical use in patients with castration-resistant prostate cancer, symptomatic bone metastases, and no known visceral metastatic disease [40]. Radium-223 is an α -particle-emitting radioisotope with a physical half-life of 11.4 days, which allows it to be shipped to practically any location that can treat patients. Radium-223 was the first α -particle therapy approved in the United States and the first nuclear-based therapy that extends survival in patients with bone metastasis, validating the potency and safety of α -particles to treat malignancy. In the phase 3 ALSYMPCA (Alpharadin in the Treatment of Patients With Symptomatic Bone Metastases in Castration-Resistant Prostate Cancer) trial, patients with prostate cancer with osseous metastatic disease treated with ^{223}Ra had increased survival and decreased bone pain [41]. The mechanism of action for ^{223}Ra is similar to that of other nuclear bone-seeking agents in that it mimics calcium and forms complexes with hydroxyapatite in remodeling bone [1]. In contrast to ^{90}Sr , the traditional β -particle-emitter used to alleviate malignancy-induced bone pain, ^{223}Ra showed increased survival in patients with osseous metastasis [41]. In addition, ^{223}Ra treatment resulted in decreased morbidity measured as increased time to initial opioid initiation and time to external beam radiotherapy [41]. Furthermore, the increased potency of ^{223}Ra coupled with its ultrashort range limits damage to surrounding tissue and allows it to be administered monthly up to 6 times with little adverse effect [40]. The success of ^{223}Ra in clinic opens an era of excitement for high-LET α -particle therapy.

Developing Approaches for Using Molecular Targeted α -Particle Therapy

Radium-223 is effective in its unconjugated state because of its affinity to areas of bone turnover, which surround osseous metastasis in prostate cancer [1]. However, because of its chemical properties, radium is difficult to conjugate to molecular delivery systems that target tumor-restricted biomarkers. Fortunately, other α -particle-emitting isotopes are available that have similar therapeutic potential as ^{223}Ra but can also be conjugated to antibodies, proteins, and other delivery systems. The most commonly used α -particle emitters that have been shown to be efficacious in clinical molecular targeting applications are ^{213}Bi , ^{225}Ac , and ^{211}At [1, 42–65] (Table 1). Although there is compelling evidence for using the targeted α -particle approach, the principal drawbacks of these radioisotopes are their availability and expense. Although these issues have somewhat stymied rapid development of α -particle therapies, the early evidence strongly supports their clinical effectiveness and safety. Furthermore, the success of ^{223}Ra is drawing more interest into the field of targeted α -particle therapies, which will likely decrease the cost of the radioisotopes and increase their availability.

Astatine-211

Astatine-211 is a cyclotron-produced α -particle emitter that has a 7.2-hour half-life [56]. It offers many attractive features for targeted radiotherapy, including quantitative α -particle emission with each ^{211}At decay, no long-lived α -particle-emitting daughter products, a half-life well-suited for use with a diversity of chemistry applications, and compatibility with a variety of carriers capable of delivering a dose to the patient. However, its availability is limited by the need for a specialized cyclotron that is present at only about 30 sites worldwide [66]. Given its half-life of only 7.2 hours, the current scarcity of ^{211}At production sites limits the ability to ship it to distant sites for radiotherapeutic applications. This supply constraint has resulted in only a very limited number of clinical trials using this promising radioisotope (Table 1). Despite this shortcoming, the many potential advantages of ^{211}At , including cost, radiochemistry experience by early adaptors, and proof-of-concept clinical trials, are spurring its development as a therapeutic α -particle emitter. In addition, ^{211}At decay also results in a 77- to 92-keV polonium x-ray, which gives targeting strategies using this α -particle-emitter a theranostic characteristic that enables noninvasive nuclear planar or SPECT of real-time biodistribution [56]. As more clinical evidence provides further proof-of-concept for the use of ^{211}At , it is assumed that the current supply bottleneck will be resolved through additional infrastructure investments.

Actinium-225

Actinium-225 is a radioisotope with four α -particle emissions, making it a very efficacious and potent choice for a nuclear payload. Actinium-225 has a half-life of 10 days and is produced as a decay product of uranium [67, 68]. In addition to emitting an α -particle, ^{225}Ac decay also results in a 440-keV gamma ray emission that can be used for imaging therapeutic biodistribution. The relatively long half-life of ^{225}Ac allows a centralized production or purification site that can ship it to potential users. In the United States, Oak Ridge National Laboratory currently purifies ^{225}Ac from uranium stockpiles for commercial use. The limiting factor for ^{225}Ac is its cost, which exceeds \$1200/mCi when including shipping costs. In addition to purifying from a uranium source, some investigators have developed a method of producing small amounts of high purity ^{225}Ac from a standard proton-beam cyclotron using very long irradiation times (7–50 hours) [69]. Despite the cost issue, the availability of this α -particle emitter allows practically any investigator to exploit the power of α -particle emitters. Furthermore, ^{225}Ac can now be easily conjugated to antibodies and peptides using standard widely available macrocyclic bifunctional chelators, which makes it appealing to groups without specialized radiochemistry expertise [70–72]. We and a limited number of other groups have been able to successfully stably conjugate ^{225}Ac to proteins and peptides without damaging the in vivo targeting characteristics of the antibody or peptide. The principal radiochemistry challenge of conjugating ^{225}Ac is the retention of the radiotoxic daughter products from decay (such as ^{213}Bi), which have diverse chemical properties and dissociate from the targeting moiety. One promising approach that can overcome this issue was described as a ^{225}Ac “nanogenerator” approach, in which the delivery system is designed to be internalized into the targeted tumor cell, where the toxic daughter elements may dissociate from the targeting molecule but will be trapped inside the cell, adding to the therapeutic effect of the ^{225}Ac

[70–74]. In addition, nanotechnology is being applied to safely sequester several daughter products during the administration of ^{225}Ac -based therapies [75–77]. It is hoped that as α -particle therapies become more commonly developed, the price for ^{225}Ac will decrease and spur further development of molecular targeted α -particle therapies.

Bismuth-213

Bismuth-213 is a short-half-life (46 minutes) α -particle emitter that is obtained from a ^{225}Ac generator. Acceptable activity can be eluted from the generator for about 10 days. The principal shortcomings of using ^{213}Bi are, therefore, its very short half-life and the same availability and cost constraints as for ^{225}Ac , which is the requisite starting material for the ^{213}Bi generator. Additional technical challenges include generator failure due to radiation damage, which increases the breakthrough of contaminants such as ^{225}Ac into the solution to be used in clinical formulation [78]. The very short half-life restricts the use of ^{213}Bi by limiting the time available to perform conjugation chemistry and inject the patient. Despite these limitations, a number of groups have used ^{213}Bi in preclinical and clinical trials showing its feasibility [42–46, 65, 79–82]. Some of these early trials indicated that used the ^{225}Ac -based nanogenerator approach described earlier may be more therapeutically efficacious compared with ^{213}Bi for antibodies because of its superior α -particle yield or decay, as well as the longer half-life of ^{225}Ac and its daughter elements, which match the longer biologic half-life of large-molecular-weight antibodies [74]. However, ^{213}Bi may have use when attached to faster-clearing agents, such as peptides or peptidomimetics. Although we are still in the early stages of α -emitter therapeutic development, the promising results obtained with ^{213}Bi indicate that it may be a viable therapeutic alternative in select applications.

Molecular Imaging of Targeted α -Particle Therapy

Molecular imaging techniques have the potential to expedite radiopharmaceutical development and translation. Although α -particle emissions themselves cannot be imaged using conventional nuclear medicine techniques, it is possible to image their biodistribution and tumor targeting using conventional nuclear medicine imaging through the detection of gamma rays that they or their daughter radionuclides emit. Furthermore, in the preclinical setting, β -emissions by daughter radionuclides can also be imaged using Cerenkov luminescence imaging. Although corrections need to be made when using both techniques to image α -particle targeting, important information can be obtained to enhance biodistribution and dosimetry studies in preclinical animal models.

SPECT can be used to aid targeted α -particle therapy development provided that the radiopharmaceutical contains an α -emitting radionuclide that results in a gamma ray emission with an energy range of 100–200 keV [83]. Several α -emitting radionuclides, including ^{223}Ra , ^{211}As , ^{149}Tb , and ^{225}Ac , result in a gamma ray emission in this optimal energy window [78]. For example, a number of small animal studies showed the use of SPECT/CT with gamma rays attributed to daughter radionuclides in the ^{225}Ac decay pathway [75, 77]. These studies used small animal SPECT/CT to validate standard biodistribution studies and illustrate the in vivo accumulation and clearance of ^{225}Ac -doped

nanoparticles targeting lung epithelium. Thus far, these imaging studies have been limited to preclinical small animal studies, and no α -emitting radionuclide has been indirectly imaged in the clinical setting.

Cerenkov radiation occurs when charged particles exceed the speed of light in a given medium [84]. This phenomenon is observed in radionuclides that decay by β -particle emission or Compton scattering and is often observed as visible light [85]. Recently, researchers have attempted to harness this radiation in an attempt to probe biologic phenomena. As a result, Cerenkov luminescence imaging has emerged as a new molecular imaging technique that is being explored as a cost-effective alternative to PET and SPECT [86]. Cerenkov luminescence imaging is an optical imaging method that uses charge coupled device cameras typically found in conventional imaging systems to detect Cerenkov radiation. Although the images produced are 2D and lower in resolution compared with PET or SPECT images, quantitative information can still be obtained to guide researchers in the early stages of radiopharmaceutical development [87–90]. To date, only the in vitro Cerenkov luminescence imaging of ^{225}Ac has been reported, but this has led to further studies to describe the origin of the light emissions associated with ^{225}Ac and other α -particle-emitting radionuclides [86, 90, 91]. Computer simulations and experimental studies show that the α -particles emitted by ^{225}Ac are of insufficient energy to produce enough Cerenkov radiation to be useful for Cerenkov luminescence imaging and attribute the majority of the observed luminescence to originate from the decay of ^{213}Bi , ^{209}Tl , and ^{209}Pb , which are daughter radionuclides produced in the ^{225}Ac decay pathway.

In addition, although the authors suggest that the use of ^{225}Ac for Cerenkov luminescence imaging of targeted α -particle therapy in vivo is valid, several points must be considered when designing experiments to produce accurate results [90, 91]. First, Cerenkov luminescence imaging will be reporting the location of the daughter products in the decay chain and not that of the ^{225}Ac . Thus, it is important to consider the tissue localization and biodistribution of the daughter products in addition to ^{225}Ac to understand the images generated. This is particularly important when considering the imaging of ^{225}Ac radiopharmaceuticals, because the recoil energy generated from the decay of ^{225}Ac to ^{221}Fr has been observed to liberate ^{221}Fr and subsequent daughter radionuclides from the original molecule. Once released, these daughter products circulate freely within the animal model and are deposited at sites of natural accumulation. Second, the measured light output from a tissue must be proportional to the activity contained in that tissue for Cerenkov luminescence imaging to be quantitatively useful for α -emitters. This dictates that time must elapse before in vivo images are acquired because some decay schemes require a period of time for the daughter products to achieve equilibrium with the parent radionuclide and luminescence to become proportional to the activity of the original radionuclide. For ^{225}Ac , this time period is estimated to be 10 hours. Finally, a further time delay can occur between the initial decay of an α -particle-emitting radionuclide and the production of Cerenkov radiation. However, those α -emitting radionuclides that show concomitant β -particle emission as part of their own decay process (as opposed to a daughter decay) do not experience such a delay and show immediate Cerenkov radiation production.

Renewed interest in targeted α -particle therapy has spurred the development of new technologies and the application of conventional imaging methods to study the delivery of α -particle radiopharmaceuticals. Although there are currently significant limitations in using molecular imaging to aid in the development of targeted α -particle therapies, continued development of techniques such as SPECT and Cerenkov luminescence imaging can provide meaningful data to improve the biodistribution and safe administration of these highly cytotoxic agents.

Conclusion

Given the promise of α -particle-based targeted therapeutics in early preclinical and clinical investigations, there has been recent interest in using this exciting approach for a large number of antibodies targeting numerous cancers. Furthermore, the parallel development of superior delivery systems that have more favorable biodistribution characteristics adds optimism that targeted α -particle therapy can efficaciously treat cancer without harming normal tissue. In addition to the α -particle emitters mentioned here that have been tested in clinical trials, additional radioisotopes with favorable characteristics are starting to be investigated. For example, ^{227}Th has a similarly long half-life (18.7 days) compared with ^{225}Ac , satisfactory radiochemistry properties, and emits five α -particles per nuclear decay. Investigators have shown the potential of using this α -particle-emitter in preclinical studies when conjugated to trastuzumab or rituximab [92–95]. Although issues regarding the daughter elements need to be further investigated, ^{227}Th can be generated from a long-term generator and may present a continuous source of radioisotope. Thus, given the promise of molecular targeted α -particle therapy in conjunction with new developments in the evolving field of biomarker targeting, there is optimism that the approval of ^{223}Ra for osseous bone metastasis in prostate cancer is just the first of many α -particle-based therapies that will show efficacy in clinic without the toxic adverse effects or induction of resistance that is seen with traditional chemotherapies.

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Fig. 1. Illustration of monoclonal antibody conjugated to chemotherapeutic agent. Potentially toxic chemotherapeutic agents can be targeted to tumor-restricted biomarkers by attaching them to specific delivery systems, such as antibodies, that bring them directly to tumor cells and spare normal tissue from their deleterious effects. (Drawing by Mintz A)

Fig. 2.

Images show comparison of clearance of radiolabeled antibody versus peptide.

A, Anterior whole-body planar scintigraphy of a 72-year-old man with suspected recurrent prostate cancer obtained 3 days after administration of 5.1 mCi (188.7 MBq) of ^{111}In capromab pendetide (ProstaScint, Cytogen) antibody shows significant residual activity in blood pool (heart and great vessels) even 3 days after administration.

B, Whole-body anterior (*left*) and posterior (*right*) planar images of a 49-year-old woman with a suspected gastrinoma obtained 4 hours after administration of 6.0 mCi (222.0 MBq) of ^{111}In pentetreotide show little visible activity seen in blood pool (in regions of heart and great vessels) only hours after administration, in contrast to what is seen with high-molecular-weight antibodies (**A**). Images also show significant renal uptake as well as clearance into bladder.

TABLE 1**Clinical Trials That Used α -Particle Therapy**

Isotope	Target, Antibody	Cancer Type	Reference
^{213}Bi	CD33, ^{213}Bi -HuM195	Chronic myelomonocytic leukemia	[42–44]
^{213}Bi	CD20, rituximab	Non-Hodgkin lymphoma	[45]
^{213}Bi	Neurokinin type-1 receptor, substance P (11-mer peptide)	Glioblastoma	[46]
^{213}Bi	NG2 proteoglycan, monoclonal antibody 9.2.27	Melanoma	[47]
^{223}Ra	Hydroxyapatite in remodeling bone, $^{223}\text{RaCl}$	Prostate cancer	[1, 48–55]
^{211}At	Untargeted, ^{211}At -human serum albumin	Carcinoma of tongue	[56–58]
^{211}At	Tenascin-C, chimeric 816 antibody	Glioblastoma	[59–61]
^{211}At	^{211}At -MX35 F(ab') ₂	Ovarian carcinoma	[62]
^{225}Ac	^{225}Ac -DOTA, HuM195	Leukemia	[63–65]

Note—HuM195 = humanized monoclonal antibody 195, MX35 = murine monoclonal antibody, F(ab')₂ = fragment antigen-binding, DOTA = tetraazacyclododecanetetraacetic acid.