INVITED COMMENTARY

Overcoming the Obstacles to Clinical Evaluation of ^{211}At-Labeled Radiopharmaceuticals

The potential for using the α-particle–emitting radionuclide ^{211}At in cancer therapy has been noted in the literature for many years (*1–7*). ^{211}At is 1 of only a few α-emitting radionuclides considered to be reasonable candidates for in vivo therapeutic use (*8*). However, it has taken several decades from the discovery of ^{211}At to begin clinical evaluation of its potential in cancer therapy. The primary reason for this long lead time is that many obstacles placed by nature and man had to be surmounted before clinical studies could be initiated. Fortunately, many of the obstacles that have prevented clinical evaluation in the past have been overcome, and the potential of this α-emitting radionuclide for therapy of cancer (endoradiotherapy) will be assessed in different radiopharmaceutical forms in the coming years. In this issue of *The Journal of Nuclear Medicine*, Zalutsky et al. (*9*) describe studies that circumvent some of the formidable challenges to entering clinical studies with ^{211}At. Although there was an earlier report of a single patient receiving human serum albumin microspheres containing ^{211}At to treat plate epithelial carcinoma (*10*), the results reported in the article by Zalutsky et al. (*9*) have led to the first clinical evaluation of an ^{211}At-labeled radiopharmaceutical. This can be considered a major triumph over the last of a series of obstacles to entering into a clinical study with ^{211}At. To place this accomplishment in perspective, one must reflect on the obstacles that had to be surmounted to begin that clinical study. Some of the highlights are described in this commentary.

^{211}At was produced in 1940 on the cyclotron at the University of California at Berkeley (*11*). The first hurdle to evaluating ^{211}At in biologic studies was manmade. Because of World War II, nearly a decade passed before in-depth in vivo evaluations were conducted. In vivo studies showed that, like radioiodine, ^{211}At was accumulated in the thyroids of rats and monkeys (*12–14*). However, it was noted that the metabolism and biologic effects of ^{211}At in rats and monkeys were significantly different. There can be little doubt that the history of ^{211}At use in cancer therapy would have been different if it had been found that ^{211}At in its free state was identical, or very similar, to radioiodine. Such a finding would have made free [^{211}At]astatide attractive for therapy of thyroid cancer (*15*). The results obtained in those early studies indicated that ^{211}At required a cancer-selective targeting agent to be used in cancer therapy.

Nature provided the next 2 major obstacles to evaluating ^{211}At in cancer therapy. First, it was not until the advent of methods to prepare monoclonal antibodies (*16*) in the 1970s that appropriate cancer-selective carrier molecules were available. Second, it was noted that, again unlike radioiodine, ^{211}At directly labeled on proteins was very unstable toward in vivo dehalogenation (*17,18*). The problem of astatinated-protein stability was circumvented by attaching the ^{211}At to a nonactivated aromatic ring (*19–21*). Indeed, Dr. Arnold M. Friedman, who (as I understand it) wanted to resurrect targeted ^{211}At therapy, in collaboration with a team of scientists at the Argonne National Laboratory (Argonne, IL) and the University of Chicago (Chicago, IL) that included Dr. Evan H. Appelman and Dr. Michael Zalutsky, reported the first stable attachment of ^{211}At to a protein in 1977. Difficulty was encountered in the ^{211}At labeling studies; full characterization of the products could not be attained because there are no stable nuclides of astatine. However, several investigations showed that the nonactivated aryl compounds could be readily astatinated through organometallic intermediates (*22–24*). Zalutsky et al. (*9*) have spent considerable effort since that time evaluating various structures of the nonactivated aromatic ring compounds and optimizing labeling conditions such that they can be used in clinical studies. Their article describes labeling conditions that were used over many years of study, but optimization of conditions for scale-up to clinical levels of ^{211}At-labeled antibody had to be conducted. It is encouraging to see that labeling yields can be obtained for high-level labeling (e.g., 2.15 GBq [58 mCi]) that are similar to those obtained for 37- to 74-MBq (1- to 2-mCi) labeling.

A manmade (but necessary) hurdle that had to be surmounted before beginning clinical studies is an assessment of the toxicity of ^{211}At. There are always questions of toxicity when α-emitting radionuclides are involved. This likely comes from the very high toxicity of the α-emitting radionuclides thorium, plutonium, and polonium. Early studies with ^{211}At raised the issue of a potential for breast cancer with free [^{211}At]astatide (*25,26*). Although there are several questions about those studies, this specter again makes it imperative that the astatine remain attached to its carrier molecule. Additionally, Cobb et al. (*27*) noted that toxicity of [^{211}At]astatide in mice

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was observed in spleen, lymph nodes, bone marrow, gonads, thyroid, salivary glands, and stomach. In a recent study, McLendon et al. (*28*) evaluated the toxicity of free astatide- and astatine-labeled antibody in rodents. They found that "the LD_{10} for [^{211}At]astatide was about 10-fold higher than the effective treatment dose for ^{211}At labeled monoclonal antibody" in rats, where LD_{10} is the lethal dose for 10% of the animals. They also found that "the LD_{10} of ^{211}At-labeled chimeric 81C6 in a mouse strain was about half that of [^{211}At]astatide" (*29*). Those results established the preclinical maximum tolerated dose of ^{211}At-labeled chimeric 81C6 and defined the target organs for toxicity (in the rodent model). The results of those studies were used to determine the starting doses for clinical studies.

The question that is often asked about the use of ^{211}At as a radionuclide for therapy is whether enough ^{211}At could be produced if clinical studies show that astatinated monoclonal antibodies effectively treat cancer. This question is fair and presents a large obstacle for clinical studies and widespread application. The amount of ^{211}At that must be produced is dependent on the quantity required per patient treatment. It is not clear at this time how much ^{211}At is required in effective cancer therapy. That quantity likely depends on the cancer type that is being targeted and the carrier molecule that is being used. Because it seems that the most likely application of this radionuclide will be to treat disseminated metastatic disease or disease retained in compartmental spaces (i.e., ovarian or brain cancer), an argument can be made that smaller quantities will be required than are needed for β-emitting radionuclides used in treating solid tumors. However, the number of patients that might be treated is staggering, so a reasonable method for large-scale production should be available. One method of large-scale preparation might be to irradiate thorium or uranium with high-energy proton beams to provide ^{211}Rn through spallation reactions (*30*). The ^{211}Rn produced could be used in a cryogenic generator system to provide ^{211}At for therapy. It has been estimated that such a system could provide curie levels of ^{211}Rn/^{211}At from each irradiation. There are, of course, issues of contamination with the problematic 8.3-h half-life of ^{210}At. It is important to note that the issue of ^{210}At contamination is not a consideration in irradiation of bismuth when an α-particle beam is used below 29-MeV current. Larsen et al. (*31*) report that irradiation at 50–60 μA for 1.5–4 h using their internal target can produce large quantities of ^{211}At (1.96–6.59 GBq [53–178 mCi]) and that the majority of that activity (1.26–3.74 GBq [34–101 mCi]) can be isolated by dry distillation in a form that can be readily used in labeling procedures. These data suggest that a potentially viable route to circumventing the problem of ^{211}At availability would be to have regional cyclotron centers using the internal targets. With this setup, large-scale production of ^{211}At could be attained and delivery of an ^{211}At radiopharmaceutical to hospitals and treatment centers could be made in a short period of time after production.

With the publication of the article by Zalutsky et al. (*9*), it appears that most of the major obstacles for investigating astatinated (intact) monoclonal antibodies have been surmounted, and it seems likely that other clinical studies will be initiated. Several other ^{211}At-labeled molecules have been investigated, or are under investigation, for use as ^{211}At therapeutic radiopharmaceuticals. Early therapy studies with ^{211}At-labeled tellurium colloid showed the potential for cure in an ascites model in mice (*32*,*33*), and more recently ^{211}At-labeled monodisperse polymer particles showed efficacy for intraperitoneal metastases (*34*,*35*). Despite the encouraging results from using nonspecific carrier molecules, it seems that, because of the short path-length of the α-particle, cancer-cell–selective targeting agents such as monoclonal antibodies are the best candidates as carriers, even when they are delivered in compartmental spaces. Other small-molecule ^{211}At-labeled radiopharmaceuticals (e.g., methylene blue (*36*), methyl-naphthoquinol diphosphonate (*37*), deoxyuridine (*38*), diphosphonates (*39*), benzylguanidine (*40*), and peptides (*41*)) are being evaluated in preclinical studies. It might be anticipated that some of those radiopharmaceuticals will also make it to clinical studies. However, it is important to note that, whereas slowly metabolized ^{211}At-labeled molecules can be evaluated in clinical studies at this time, more rapidly metabolized carrier molecules still present a significant obstacle to developing new ^{211}At radiopharmaceuticals. This is true because the stability of ^{211}At can be compromised when it is attached to a rapidly metabolized molecule. Although a method of stabilizing ^{211}At under metabolic conditions presents yet another major challenge, it should be possible to surmount this obstacle as well.

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