Is Actinium Really Happening?

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The most recent survey (*1*) related to α-radiotherapy development showed that 27 molecules labeled with ^{225}Ac are presently under development, among which 13 have already reached human test level. The first ^{225}Ac-labeled molecule has entered the clinical phase III stage (*2*) and might reach the market by 2028. These molecules cover the most important indications that are studied with β-emitting radionuclides, but it is obvious that each single ^{177}Lu-labeled drug will be explored as a ^{225}Ac-labeled analog. Among the 35 ^{177}Lu-labeled molecules that have already reached the clinical stage, an estimated dozen have a high chance to reach the market before 2030, not even taking into account all the generics. Actinium-labeled drugs will follow the same trend, with a delay of about 5 y. A global target of half a million patients represents only 1% of the 5-y prevalence of cumulated cancers (Global Cancer Observatory; https://gco.iarc.fr), which remains realistic in terms of share of the market compared with surgery, external radiotherapy, or chemotherapy.

Evaluation of further needs is based on today's average patient dose of 100 kBq/kg. At least 10–12 MBq at end of bombardment must be produced per dose, taking into account losses during handling and transport and labeling yields. On the basis of an average of 3 doses for a full treatment, each patient will need a total of 30–36 MBq of ^{225}Ac at end of bombardment. In other words, 3,000 GBq at end of bombardment would be sufficient to treat 100,000 patients each year. Industry will have to guarantee capacity for 5–6 times this yearly amount by 2032.

Over the past few years, several large investments were made in 5 different technologies to develop large-scale production of ^{225}Ac. The different routes have been described in the literature (*3,4*). Already-operating sites and new-development units for technologies A–E are summarized in Table 1 with their production capacities.

THE 5 TECHNOLOGIES

Technology A

Carrier-free ^{225}Ac has been produced through the natural decay of ^{229}Th. The 3 sites that can presently produce high-quality ^{225}Ac (United States, Russia, and Germany) will not significantly increase their production capacity. Only Russia is planning such capacity improvement, but the additional amount will remain insignificant compared with the future demand. Fortunately, the war has not (yet) altered access of ^{225}Ac to U.S. patients in clinical trials from Russian sources. In the United States, the company TerraPower obtained access to larger amounts of ^{229}Th that still need to be purified and plans stepwise progress over the next 10 y, although the output will still be only a small fraction of the future need. If alternative routes become successful, this generator route will not remain competitive, but for the time being, it remains the largest source of very clean ^{225}Ac.

Technology B

The ^{232}Th activation programs (United States and Canada) have progressed well. A very high capacity can be reached, and the technology might allow production of several terabecquerels per year. Unfortunately, this product remains contaminated with ^{227}Ac (half-life, 21.8 y). The mixture can be used for development purpose up to clinical phase II without limitation, but cleaner forms of ^{225}Ac will be preferred in routine applications and as marketed forms. Specifications limit the ^{227}Ac threshold to 2%, a level that was demonstrated not to affect patients (*5,6*). Release of radioactive waste from patients in the waste tanks of hospitals is the real issue. Although European authorities will probably recommend, if not constrain, users to avoid ^{227}Ac, in the United States this radionuclide needs to be added to the radioactive waste and will directly affect the level of the decommissioning financial assurance that is supposed to be in place at the user's end. A similar situation was experienced in the past when the industry was given a choice between no-carrier-added ^{177}Lu and ^{177m}Lu-contaminated carrier-added ^{177}Lu. ^{225}Ac/^{227}Ac might find better applications in the development of ^{225}Ac/^{213}Bi generators, provided that the industry becomes interested in ^{213}Bi.

Technology C

In the thorium activation process B, ^{225}Ra as a by-product can easily be separated from the mixture, allowing indirect access to clean ^{225}Ac through its decay. Unfortunately, yields are limited to only 10% compared with the ^{225}Ac/^{227}Ac mix, generating high levels of waste and limiting financial attractiveness.

Technology D

Accelerator production is possible by irradiating ^{226}Ra targets using small cyclotrons. Several large-scale production sites are now under construction, supported by companies in the United States and Europe. Eventually, large amounts of ^{225}Ac might be produced per week, in theory more than 4 TBq a month (*7*), but realistically a tenth of this figure would allow us to stay on the safe side, with cooling of larger targets becoming the limiting factor.

Technology E

More recent developments have shown that photoconversion technology not only is a way to generate very clean ^{225}Ac but also

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TABLE 1
Technologies Under Development and Operating Sites for ^{225}Ac Production, Including Estimated Present and 2032 Capacities

Technology	Source	Yearly production capacity (GBq/y/site) 2023	2032	Total (GBq/y) in 2032	Comment
A: [(^{233}U→) ^{229}Th→^{225}Ac] (generator)	ORNL, United States	26	26	Up to 3,000 [80]	Highest quality of *nca* ^{225}Ac; may enter price competitivity
	IPPE, Russia	37 (est.)	150 (est. 2025) to 300 (est. 2030)		
	JRC-ITU, Germany	11	11		
	TRIUMF, Canada	0.4	0.4		
	TerraPower, United States	>10	≤2,700		
	Pantera, Belgium	0	>70		TerraPower source
B: [^{232}Th(p,x)^{225}Ac+^{227}Ac] (high-energy accelerator)	BNL/ORNL LANL; Tri-Lab, United States	16.7	Potential, >3,700	>9,000 [>240]	Contaminated with ^{227}Ac (0.2% EOB - ~1.5% at calibration); not suitable for large scale routine use
	CNL/TRIUMF, Canada; BWXT/ITM, United States/Germany	>1	Idem >3,700		
	INR, Russia		≤1,000		
	SpectronRx, United States	>1	>200		
	Others: Arronax, France; IsoDar, Japan; CIAE, China	First GBq in 2024	Potential, >200 each		
C: [+ … +^{225}Ra→^{225}Ac] (as side product)	~10% of above; CNL/TRIUMF, Canada	0.3	>370 (theory)	>370 [>10]	High level of waste - expensive
D: [^{226}Ra(p,2n)^{225}Ac] (cyclotron)		First GBq		>4,500 [>120]	Additional sites under evaluation in other countries (Asia)
	SpectronRx, United States	2023	>500		
	Ionetix, United States	2023	1,900		
	Eckert&Ziegler, Germany	2024	550		
	Alfarim, Netherlands	2025	450–850		
	N-MediPhysics, Japan	>2023	>500		
	KIRAMS, South Korea	>2025	>500		
D: [^{226}Ra(d,3n)^{225}Ac] (linear accelerator)	Nusano, United States		≤160,000		Under evaluation
E: [^{226}Ra(γ,n)^{225}Ra→^{225}Ac] (photoconverter)	NorthStar, United States	2023	3,700–15,000	>37,000 [>1,000]	Rhodotron: *nca* ^{225}Ac
	Pantera, Belgium	2027	3,700–5,000		
	TerraPower, United States	2029	3,700–5,000		
	Niowave, United States	2023	≤18,000		Linac: *nca* ^{225}Ac
	Hitachi, Japan	>2024	>3,700		
F: [^{226}Ra(n,2n)^{225}Ra→^{225}Ac] (n from d on beryllium target)	Nusano, United States		≤44,000		Under evaluation

ORNL = Oak Ridge National Laboratory; *nca* = no carrier added; IPPE = I.I. Leypunsky Institute of Physics and Power Engineering, Obninsk; est. = estimated; JRC-ITE = Joint Research Centre–Institute for Transuranium Elements; TRIUMF = TRI University Meson Facility; BNL = Brookhaven National Laboratory; LANL = Los Alamos National Laboratory; EOB = end of bombardment; CNL = Canadian Nuclear Laboratories; BWXT = BWX Technologies Inc.; ITM = Isotope Technologies Munich SE; INR = Institute for Nuclear Research of the Russian Academy of Science; CIAE = China Institute of Atomic Energy; KIRAMS = Korea Institute of Radiological and Medical Sciences.

Data in brackets are curies.

should allow large-capacity production. Facilities are under construction in the United States and Europe.

ISSUES TO BE SOLVED

Even if high capacity and reliable access to ^{225}Ac is confirmed from 2025 on, production of actinium still raises a series of other issues, some of which are on their way to being solved.

Access to Larger Amounts of ^{226}Ra

Although access and handling of ^{232}Th does not seem to be an issue, access to larger amounts of ^{226}Ra remains questionable. Most of the companies are on their way to finding a solution, either by getting access to domestic (waste) stocks or by extracting radium from older devices (e.g., paintings, radiotherapy tools, and older brachytherapy material). In the worst case, this issue should also be solved by 2025.

Need for Additional Safety Investments

Handling of ^{226}Ra is a more complex issue because this radionuclide generates the gas ^{222}Rn, which is difficult to store and trap. The increase in patients will proportionally lead to a higher need for radium and higher production of radon, leading to the need for additional safety investments.

Risk of Explosion and Contamination

Cyclotron and photoconversion technologies may face the risk of explosion of the radioactive radium target as cooling will remain difficult and the limiting factor, leading to potential contamination with long-half-life radionuclides. The increase in capacity will therefore be performed stepwise, and the upper limit remains theoretic.

Potential Toxicity and Limited Therapeutic Efficacy

^{225}Ac is an α-emitter that decays through a 6-step cascade to stable ^{209}Bi, releasing consecutively 4 α- and 2 β-particles. Recoil effects and the restricted capacity of chelators to trap decay products limit therapeutic efficacy to the first emitted α-particle. The additional α- and β-particles released by the daughter radionuclides decay elsewhere in the body. ^{223}Ra shows a similar profile, and the associated drug (Xofigo) was approved by the authorities without a request for additional studies. Potential toxic effects simply define the level of the maximum tolerated dose.

Contamination Issues

It is still not clear whether patients eventually will be handled on an outpatient basis or will be required to stay in shielded rooms, but patients treated with ^{225}Ac (half-life, 9.92 d) cannot be kept sufficiently long at therapeutic centers to collect all their waste until full decay. Releasing this waste in nature is not a problem if the number of treated patients remains low. The situation becomes different if millions of doses are used yearly and a fraction is disseminated in nature. We yet have a few years for the authorities at the national level to think seriously about this issue, which is not specific to ^{225}Ac and will—over the long term—also affect other long-half-life radionuclides, including ^{131}I, ^{177}Lu, and ^{161}Tb (*8*). This issue creates an opening for a next generation of radiotherapeutic agents with shorter half-lives such as ^{67}Cu, ^{211}At, and ^{212}Pb, but this is another story.

CONCLUSION

Altogether, the worldwide ^{225}Ac production capacity by 2032, estimated largely above 25 TBq (670 Ci), should be sufficient to produce at least 2 million patient doses a year. With an additional investment remaining below $100 million (e.g., accelerator), another 300,000 doses could be produced per new site. The situation is much more comfortable than for ^{177}Lu and ^{161}Tb, for which access to reactors will soon become the bottleneck. In the meantime, ^{225}Ac-labeled radiopharmaceuticals are just the beginning of a success story spanning 15-plus years.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

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