Targeted $\alpha$ therapy with $^{213}$Bi and $^{225}$Ac

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Abstract. The molecularly targeted treatment of cancerous tumors by the alpha-emitting radionuclides $^{213}$Bi and $^{225}$Ac has shown remarkable efficacy in clinical trials. Ultimately, this treatment option will be applicable to a wide range of cancers and other diseases, subject to the development of specific radioligands. Currently $^{225}$Ac is mainly being produced from the decay of existing stocks of $^{229}$Th. The expected wider application for radiotherapy will require many orders of magnitude more radionuclide than can currently be produced. Consequently, various alternative production methods are being pursued.

1. Introduction
In systemic radiotherapy and imaging, the supreme challenge consists in effectively targeting radionuclides to diseased cells. To achieve high sensitivity and high specificity, drugs must effectively seek out affected tissue while doing as little damage as possible to healthy organs. Starting in the 1940s, the first radiopharmaceuticals made use of some elements’ natural targeting to certain organs or cancer cells. For instance, $^{32}$P ($\beta^-$, $T_{1/2} = 14.3$ d) was employed to target cancer cells in chronic myeloid leukemia [1], because phosphorus is an active participant in the metabolism of white blood cells.

Malignant cells are often physiologically more active than healthy cells. This property was first exploited by functional targeting in the 1970s [2]. In this modality, a glucose analog is doped with a $\beta^+$- or $\gamma$-emitting nuclide, for instance $^{18}$F ($\beta^+$, $T_{1/2} = 1.8$ h) or $^{99m}$Tc ($\gamma$, $T_{1/2} = 6.0$ h). In the patient, the modified glucose is mainly accumulated in diseased cells, which have an increased metabolism. The decay of the radionuclides is then detected externally, and a three-dimensional image of the patient is obtained by positron emission tomography (PET) or single-photon emission computed tomography (SPECT).

More recently, the molecular targeting of radiopharmaceuticals has opened new avenues for radiotherapy and imaging. It is based on radioligands – either antibodies, antibody fragments, or peptides – which bind to specific cancer cells. Doped with a radionuclide, the ligand transports its payload to the target, where it decays to fulfill its therapeutic or imaging function. Damage to healthy cells is strongly reduced as the portion of the drug that doesn’t bind to receptors is quickly evacuated from the body. Molecularly targeted therapy and imaging is applicable to a wide range of diseases, limited only by the development of suitable radioligands.

Targeted therapy with alpha-emitting radionuclides (targeted alpha therapy – TAT) has several advantages compared to conventional beta therapy: First, as alpha particles pass through tissue, they deposit a larger energy per unit distance than electrons. This makes double-strand breaks to tumor cells’ DNA more likely and thus has a higher probability of causing apoptosis.
Figure 1. Decay chain of $^{225}$Ac, neglecting branching ratios with 2% probability or less. The alpha therapy radionuclides discussed in this paper are highlighted in red.

Over the last few years, two alpha emitters that are part of the decay chain of $^{233}$U have been identified as promising radionuclides for cancer therapy (see Fig. 1). $^{225}$Ac ($T_{1/2} = 9.9$ d) decays via four alpha and two beta decays. The alpha energies range from 5.8 to 8.4 MeV with a total deposited alpha energy of 27.6 MeV. In contrast, the shorter-lived $^{213}$Bi ($T_{1/2} = 45.6$ min) decays by one alpha and two beta decays, with an alpha energy of 8.4 MeV. It can be conveniently produced on site from a $^{225}$Ac generator. The tissue ranges of all alpha particles from these decays do not exceed 85 $\mu$m. Both nuclides ultimately decay to the (quasi-)stable $^{209}$Bi.

2. Clinical experience with $^{213}$Bi and $^{225}$Ac

During the last two decades, a number of clinical tests have been conducted in Europe and worldwide in the framework of “compassionate use,” which governs the use of not-yet-approved drugs in exceptional circumstances. A summary of clinical experience with $^{213}$Bi and $^{225}$Ac is shown in Table 1. The radionuclides for most studies listed in the table (except Ref. [3] and, partially, Refs. [4–7]) have been provided by JRC Karlsruhe. The $^{213}$Bi and $^{225}$Ac produced at JRC have been demonstrated to be of high chemical purity and to be safe for administration to humans following preparation according to established protocols.

Since $^{213}$Bi is a daughter of $^{225}$Ac, it can be conveniently provided in the form of a generator, i.e., an ion exchange column loaded with $^{225}$Ac. Owing to this advantage, $^{213}$Bi was the first to be used in clinical trials. To date, more than 200 patients have been treated with $^{213}$Bi in combination with radioligands targeted to leukemia [4, 5], lymphoma [8], melanoma [9–11], bladder cancer [12, 13], glioma [6, 14, 15], and neuroendocrine tumors [7]. More recently, $^{225}$Ac has also been administered directly, in conjunction with specific carriers to target leukemia [3], glioma [6], neuroendocrine tumors [16], as well as prostate cancer [17–20].

Studies on several cancer types (leukemia, glioma and neuroendocrine tumors) have been conducted both with $^{213}$Bi and $^{225}$Ac. Due to the vastly differing half-lives, the delivered doses cannot be directly compared. For a given administered dose, the initial activity simply scales with the inverse of the half-life of the radionuclide. However, the dose delivered to the target tissue also depends on the biokinetics, the stability of the radioligand, and several other factors. The administered doses were optimized to deliver a maximum effect while keeping side effects, as determined by blood counts and biochemical profiles, to acceptable levels.

Compared with conventional treatments such as chemotherapy or beta radiotherapy, TAT
has shown improved benefit for patients while reducing unwanted side effects. Current (limited) clinical evidence suggests $^{225}$Ac to be at least as effective as $^{213}$Bi at the maximum tolerable dose. However, less than 1/10 of the quantity of $^{225}$Ac is required to deliver the same dose as compared with generator-produced $^{213}$Bi [21]. Hence, from the point of view of cost and available substance (see below), direct use of $^{225}$Ac is favorable, except in cases where the short half-life of $^{213}$Bi better matches a radioligand’s biokinetics.

3. Demand and supply of $^{225}$Ac

The $^{225}$Ac radionuclide substance has historically been produced from the natural decay of $^{229}$Th ($T_{1/2} = 7920$ a), by harvesting the ingrown daughter every $\approx 8$ weeks. Pure $^{225}$Ac is radiochemically extracted in a two-step ion exchange and extraction chromatography process. Oak Ridge National Laboratory (ORNL) [22], the Institute for Physics and Power Engineering (IPPE) [23] and JRC Karlsruhe [24] own stocks of $^{229}$Th and regularly produce $^{225}$Ac by this process. A total amount of 70 to 75 GBq of $^{225}$Ac is produced annually, enabling all preclinical work and clinical trials with $^{213}$Bi and $^{225}$Ac to date. However, the projected demand – given the prevalence of cancer types against which TAT has been shown to be effective [25] – is many orders of magnitude higher. Hence, several alternative routes for $^{225}$Ac production have been investigated. These are (1) the medium-energy proton irradiation of $^{226}$Ra using the reaction $^{226}$Ra($p,2n$)$^{225}$Ac; (2) the spallation of uranium (or thorium) targets by high-energy (0.6–2 GeV) protons via the reaction $^{nat}$U($p,x$)$^{225}$Ac; (3) the transmutation of $^{226}$Ra to $^{229}$Th by thermal neutrons using three successive ($n,\gamma$) reactions; and (4) the transmutation of $^{226}$Ra to $^{225}$Ra by ($n,2n$) or ($n,\gamma$) reactions.

The first of these was pioneered at JRC Karlsruhe. With the aim of measuring reaction cross-sections and yields, targets containing $\mu g$ to $mg$ amounts of $^{226}$Ra were produced. Thin targets containing 12.5 $\mu g$ of radium chloride evaporated onto a silver foil were welded into gas-tight silver capsules, placed in a water-cooled holder and irradiated at up to 28 MeV energy at the Karlsruhe cyclotron [26]. Cross-sections for proton energies from 9 to 25 MeV were measured by chemically separating dissolved target layers. The maximum cross-section was found to be 710(70) mb at a proton energy of $\approx 16.8$ MeV.

The total yield was measured by irradiating thick targets containing 30 mg of $^{226}$Ra each in a barium chloride matrix (see Fig. 2). After irradiation with 100 $\mu A$ of protons for 1 day, 5 GBq of $^{225}$Ac were produced, about 1/3 the calculated maximum thick-target yield [27]. Extrapolating this to round-the-clock production at a cyclotron, about 1 TBq or 100 000 patient doses per year could be manufactured at a single facility. This production path would therefore be adequate

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Table 1. Overview of clinical experience with $^{213}$Bi- and $^{225}$Ac-labeled radioligands.

| Cancer type       | Radioconjugate | No. of patients | Refs. |
|-------------------|----------------|-----------------|-------|
| Leukemia          | $^{213}$Bi- $^{225}$Ac - HuM195mAb | 49 [4, 5] | |
|                   | $^{225}$Ac-   | 36 [3] | |
| Lymphoma          | $^{213}$Bi- anti-CD20-mAb | 12 [8] | |
| Melanoma          | $^{213}$Bi- 9.2.27mAb | 54 [9–11] | |
| Bladder cancer    | $^{213}$Bi- anti-EGFR-mAb | 12 [12, 13] | |
| Glioma            | $^{213}$Bi- $^{225}$Ac - Substance P | 68 [6, 14, 15] | |
| Neuroendocrine    | $^{213}$Bi- $^{225}$Ac - DOTATOC | 25 [7] | |
| tumors            | $^{225}$Ac-   | 19 [6] | |
| Prostate cancer   | $^{225}$Ac- PSMA-617 | $>300$ [17–20] | |
for covering a significant portion of the projected worldwide demand of $^{225}\text{Ac}$. A large number of suitable cyclotron facilities is available in Europe and worldwide.

To conclude, targeted alpha therapy with the alpha emitters $^{213}\text{Bi}$ and $^{225}\text{Ac}$ has proven to be a promising treatment option for those cancers where suitable radioligands have been developed. As a prerequisite for approval and widespread use, new production routes are being explored. JRC Karlsruhe is investigating cyclotron production via the $^{226}\text{Ra}(p,2n)^{225}\text{Ac}$ reaction.

References

[1] Craver L F 1942 Bull. N.Y. Acad. Med. 18 254
[2] Reivich M, Kuhl D, Wolf A et al. 1979 Circ. Res. 44 129
[3] Berger M, Jurcic J, Scheinberg D et al. 2017 10th International Symposium on Targeted Alpha Therapy (Kanazawa, Japan, 30 May – 1 June 2017) p 22 (abstract)
[4] Jurcic J G, Larson S M, Sgouros G et al. 2002 Blood 100 1233
[5] Rosenblat T L, McDevitt M R, Mulford D A et al. 2010 Clin. Cancer Res. 16 5303
[6] Krolicki L, Bruchertseifer F, Kunikowska J et al. 2017 10th International Symposium on Targeted Alpha Therapy (Kanazawa, Japan, 30 May – 1 June 2017) p 24 (abstract)
[7] Kratochwil C, Giesel F L, Bruchertseifer F et al. 2014 Eur. J. Nucl. Med. Mol. Imaging 41 2106
[8] Schmidt D, Neumann F, Antke C et al. 2017 4th Alpha-Immunotherapy Symposium (Düsseldorf, Germany, 28–29 June 2004) p 12 (abstract)
[9] Allen B J, Raja C, Rizvi S M et al. 2005 Cancer Biol. Ther. 4 1318
[10] Raja C, Graham P, Abbas Rizvi S M et al. 2007 Cancer Biol. Ther. 6 846
[11] Allen B J, Singla A A, Rizvi S M et al. 2011 Immunotherapy 3 1041
[12] Autenrieth M E, Horn T, Kurtz F et al. 2017 Urologe 56 40 (article in German)
[13] Autenrieth M E, Seidl C, Bruchertseifer F et al. 2018 Eur. J. Nucl. Med. Mol. Imaging 45 1364
[14] Kneifel S, Cordier D, Good S et al. 2006 Clin. Cancer Res. 12 3843
[15] Cordier D, Forrer F, Bruchertseifer F et al. 2010 Eur. J. Nucl. Med. Mol. Imaging 37 1335
[16] Kratochwil C, Bruchertseifer F, Giesel F et al. 2015 J. Nucl. Med. 56 1232 (abstract)
[17] Kratochwil C, Bruchertseifer F, Giesel F et al. 2016 J. Nucl. Med. 57 1941
[18] Kratochwil C, Bruchertseifer F, Rathke H et al. 2017 J. Nucl. Med. 58 1624
[19] Kratochwil C, Bruchertseifer F, Rathke H et al. 2018 J. Nucl. Med. 59 795
[20] Sathekge M, Bruchertseifer F, Knoesen O et al. 2019 Eur. J. Nucl. Med. Mol. Imaging 46 129
[21] Allen B J 2017 Australas. Phys. Eng. Sci. Med. 40 369
[22] Boll R A, Malkenuis D and Mirzadeh S 2005 Appl. Rad. Isotop. 62 667
[23] Samsonov M D, Nerzin N A, Podsohlyaev D et al. 2017 10th International Symposium on Targeted Alpha Therapy (Kanazawa, Japan, 30 May – 1 June 2017) p 97 (abstract)
[24] Apostolidis C, Molinet R, Rasmussen G and Morgenstern A 2005 Anal Chem. 77 6288
[25] Ferlay J, Stelianova-Foucher E, Lortet-Tieulen J et al. 2013 Anal Chem. 49 1374
[26] Apostolidis C, Molinet R, McGinley J et al. 2005 Appl. Radiat. Isot. 62 383
[27] Morgenstern A, Abbas K, Bruchertseifer F and Apostolidis C 2008 Curr. Radiopharm. 1 135