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General Review

Targeted alpha and beta radiotherapy: An overview of radiopharmaceutical and clinical aspects

Un état des lieux des aspects radiopharmaceutiques et cliniques de la radiothérapie vectorisée par émetteurs alpha et bêta

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Abstract

For many years, the role of internal radiotherapy has remained limited to certain historical indications such as thyroid cancers or to academic medical research. However, the recent recognition of theranostics and targeted therapies as one of the cornerstones of the modern concept of personalized medicine, has participated in the promotion of new developments for beta and alpha radiotherapy. In this paper, we will review the emerging radionuclides, radiopharmaceutical developments and advances, as well as the clinical successes that have been made in past few years. The results obtained, for some very promising, could herald in a new era for nuclear medicine. However, as presented in this review, in order to fully exploit its potential, and not to remain static as a promising or emerging therapy, the entire field of nuclear medicine must invest in the implementation of well-designed prospective and comparative studies for targeted radiotherapy.

Keywords: Targeted radiotherapy; Radiopharmaceutical; Clinical

Résumé

Pendant longtemps, la place de la radiothérapie interne est restée limitée à certaines indications historiques telle que les cancers thyroïdiens ou à une recherche académique confidentielle. Cependant, la reconnaissance récente des thérapies ciblées et des approches théranostiques comme éléments clés du concept moderne de médecine personnalisée, a participé à la promotion de nouveaux développements en radiothérapie vectorisée alpha et bêta. Cette revue se propose de faire le point sur les principales avancées obtenues ces dernières années concernant les radioisotopes émergeants, les développements radiopharmaceutiques ainsi que leur transposition en clinique. Les résultats obtenus, pour certains très prometteurs, pourraient annoncer une nouvelle ère pour la médecine nucléaire. Cependant, comme présenté dans cette revue, pour exploiter pleinement son potentiel et ne pas rester une thérapie prometteuse ou émergente, l'ensemble de la communauté de médecine nucléaire doit investir dans la mise en œuvre d'études prospectives et comparatives bien conçues pour la radiothérapie ciblée.

Mots clés : Radiothérapie vectorisée ; Radiopharmaceutiques ; Clinique

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1. Introduction

One hundred years ago, Paul Ehrlich who is considered the father of chemotherapy, postulated his receptor theory and left to posterity the ''magic bullet concept'' based on the ability of a drug to go directly to its target while sparing healthy tissues. The basics of targeted therapy were laid down, but it then took a century of scientific and medical advances to envisage, especially through work on tyrosine kinase inhibitors or on monoclonal antibodies, the completion of this concept in chemotherapy in the late 1990's [1–4]. Meanwhile nuclear medicine was born and as soon as the 1940s, the first patients with metastatic thyroid cancer were able to benefit from iodine internal radiotherapy. Like Mr. Jourdain in Molière's play, nuclear medicine physicians and radiopharmacists unknowingly used theranostics and targeted therapies, well before the rest of the medical community. In fact, radiopharmaceuticals that have been administered to patients for almost 80 years, are the combination of a pharmaceutical drug able to target a specific organ, tissue, cells or receptor, and a radioisotope allowing, by its emitting properties, diagnostic or therapeutic applications.

For some time, the role of internal radiotherapy has remained limited to certain historical indications such as thyroid cancers or to academic medical research. However, the emergence and recent recognition, by the entire medical community and the pharmaceutical industry, of theranostics and targeted therapies as one of the cornerstones of the modern concept of personalized medicine [5], has prompted the advancement of new developments for beta and alpha radiotherapy. The results obtained, for some very promising, could herald in a new era for nuclear medicine, which is beginning to position itself, in certain indications, as a credible therapeutic option in contrast to chemotherapy and external radiotherapy. In this paper, we will review emerging radionuclides, radiopharmaceutical developments and advances, as well as the clinical successes that have permitted the metamorphosis of the previously confidential internal radiotherapy into the promising targeted radiotherapy.

2. Part 1: radiopharmaceutical aspects

2.1. Radionuclides

2.1.1. Alpha-emitters

From the 100th alpha existing radionuclides, only less than 10 have been introduced in clinical trials for targeted alpha therapy (TAT). Their principal physical characteristics are detailed in Table 1. Choice of suitable radioisotope is a function of multiple criteria: half-live, decay scheme, energy recoil, associated emitting, chemical properties and last but not least availability.

Among them, Actinium-225 is characterized by a rapid decay cascade, leading to stable Bismuth-209 (Table 1) that make it a potential candidate for clinical applications [6]. Actinium-225 can be obtained either from the decay of ^{233}U or by proton irradiation of Ra-226 in a cyclotron through the reaction ^{226}Ra(p,2n)^{225}Ac [7]. Actinium-225 can be also be used as a parent radionuclide for the production of a ^{225}Ac/^{213}Bi generator [8,9] or used directly for the radiolabelling of targeting constructs [10,11].

Radium-223 is also characterized by multiple alpha decay and a long physical period (11.4 days) that provides it with interesting characteristics for radiotherapy. Its production for clinical use involves ^{227}Ac and ^{227}Th isolation from ^{231}Pa [12,13]. However, the limited availability of the source of ^{231}Pa has recently led to the development of alternative production techniques based either on the isolation of the Actinium-227 by-product from the cyclotron production of Actinium-225 [12], or after isolation of ^{227}Ac provided from Actinium-227/ berylium-227 generator sources [14].

The main disadvantage of 225Ac and 223Ra, apart from their limited availability, is the fact that that recoil energy of the nuclei of these two radionuclides and different chemical properties of daughter's isotopes decrease the stability of radiolabelled constructs.

Bismuth-213 and 212 are both characterized by a short period of approximately one hour, a generator production and only one alpha emission. Bismuth-213 can be eluted from a ^{225}Ac/^{213}Bi generator in which ^{225}Ac is adsorbed onto a cation-exchange resin [15]. In addition to alpha emission, a gamma emission occurs from bismuth-213 decays (Table 1) that allows biodistribution, imaging or subsequent dosimetry studies. Bismuth-212 can also be eluted from a ^{224}Ra generator [16]. Owing to their short half-lives, the main drawbacks of these two radionuclides are that the entire processing of radiolabelling and quality control must be performed in a very short time and that the used targeting constructs must allow for rapid tumor targeting. Lead-212, the father of Bismuth-212, has been used for in vivo generated bismuth-212 in order to solve this problem but the recoil energy of Lead-212 (128 keV) must take in account in the choice of the bifunctional chelating agent (BCA) in order to avoid non-specific irradiation of healthy tissues.

Astatine-211 is unique compared to other alpha-emitters used for TAT. First, its production is not based on a decay way but obtained by cyclotron production through an (α,2n) reaction on a Bismuth-209 target [17]. Second, its chemical properties and the subsequent radiolabelling chemistry are similar to heavy halogen like iodine, which permits to consider Astatine-211 in many applications. Third, its physical half-life is short (7.2 hours) but more favorable than that of Bismuth-213. All of its characteristics make Astatine-211 a candidate of choice for TAT [18,19]. Despite the great potential of Astatine-211 for TAT and its relatively low cost of production, its current availability is low due to lack of accelerator capable of irradiating a target with an alpha-particle beam at 28 MeV [17,20]. To circumvent this issue an alternative way of production of Astatine-211 through a ^{211}Rn/^{211}At generator has been recently proposed and validated for preclinical studies [21].

2.1.2. Beta-emitters

The use of beta-emitters for targeted radiotherapy with radionuclide such as Iodine-131, Phosphorus-32 or Strontium-89 goes back to the origins of nuclear medicine [5]. Currently,