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Review

Radiotheranostics: Recent advancements and a strategy for future growth

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Abstract

Radiotheranostics, injectable radiopharmaceuticals having anticancer activity, have advanced rapidly in the last decade. Although various formulations have been approved for human use, further radiopharmaceuticals are projected to be integrated into clinical practice within the next five years, potentially giving innovative therapy options for patients. Despite these advancements, other obstacles persist, such as logistics, supply chain, regulatory constraints, and education and training. This study intends to highlight recent advances in the area, inform practitioners about the value of radiotheranostics, and establish a framework for future development. Multidisciplinary methods to clinical trial design and therapy administration will be critical for the further development of this developing therapeutic modality.

Keywords: *Oncology, Radiothernostics, discovery, thyroid cancer, cancer stem cells.*

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Introduction

Radiotheranostics is a combination of diagnostic and therapeutic radiopharmaceuticals that can be used to detect and treat diseases, including cancer. The discipline has grown quickly over the last decade, thanks to the discovery of new radiopharmaceuticals, enhanced imaging tools, and a better knowledge of how radiotheranostic therapy can be utilized to customize cancer treatment. Radiotheranostics has advanced in part due to the introduction of novel radiopharmaceuticals, which are molecules that combine a radioactive isotope with a targeted molecule. These radiopharmaceuticals can be employed in both diagnostic and therapeutic applications[1]. PSMA-targeted radiopharmaceuticals, such as PSMA-617, have showed promise in the diagnosis and treatment of prostate cancer, whilst radiolabeled somatostatin analogs have been used to diagnose and treat neuroendocrine tumors (DOTATATE).

Radiotheranostics is perhaps the most clinically advanced application of theranostics, with many developments and emerging opportunities[2]. A key aspect of radiotheranostics is that the selection of patients for radiotargeted treatments is based on imaging of the same target area; therefore, imaging and therapeutic intervention are closely linked. The concept of radiotheranostics has been around for more than 70 years, prime examples include using different forms of radioactive iodine to diagnose (eg, I) and treat (eg I) thyroid cancers.With radioactive iodine, metastatic thyroid cancer was transformed from a disease with poor outcome to a disease with about 85% overall survival[3].Nowadays, radiotheranostics is at a point of change, and is moving into the mainstream of cancer therapeutics. The main goals of radiotheranostic indications have been to stabilise end-stage disease that is refractive to other treatments and to improve quality of life in these patient populations.

Early clinical trials have improved outcomes for patients with otherwise untreatable prostate and thyroid cancers, as well as neuroendocrine tumours. Future objectives include treating early-stage cancer through targeted

intervention and reducing the side-effects of systemic radiotherapy[4]. Several radiopharmaceuticals that aim to meet these objectives are in development for cancer treatment Radiotheranostics are also being explored for non-cancer applications, such as Y-silicate joint injections (radiation synovectomy) for severe arthritis[5]. A number of new radioisotopes are expected to further improve the therapeutic window and efficacy (mainly for cancer), and image-guided interventional strategies are poised to deliver therapeutics locally with high precision[6].

Radiotheranostic pairs

A radiopharmaceutical consists of three components: the radionuclide (with diagnostic and/or therapeutic properties), a chelator (which links the radionuclide to the ligand/probe), and the ligand/probe (which targets a cancer-specific molecular marker on the tumor cell with high affinity). Sometimes, a radionuclide by itself can serve as a radiopharmaceutical without the need for a chelator or radiolabeling. The purest concept of a 'theranostic pair' consists of a chemically and structurally identical (or nearly identical) probe labeled with either a diagnostic or therapeutic radionuclide. This ensures targeting of the same molecular marker for diagnostic imaging and molecular targeted treatment[7].

Radiolabeling is a critical step in the synthesis of a radiopharmaceutical since the receptor binding affinities may be negatively affected by a decreasing degree of similarity between the diagnostic and therapeutic molecule. In that sense, the 'perfect' theranostic pair would be two isotopes of the same element[8]. The prime example is radioiodine, where for instance 123I (single photon emitter) or 124I (positron emitter) can be used for diagnostics and 131I (beta emitter) for treatment of thyroid diseases. These isotopes are chemically 'identical', and only differ in their emissions and physical half-lives, which is favorable for their respective purposes. The diagnostic counterpart can be performed by employing either single photon emission computed tomography/computed tomography (SPECT/CT) or more commonly used positron emission tomography either with computed tomography (PET/CT) or magnetic resonance imaging (PET/MRI) to obtain molecular diagnostic images. The chosen radiopharmaceutical is either a gamma emitter for SPECT or a positron emitter for PET[9-10].

Both gamma and positron emitting radiopharmaceuticals have high tissue absorption, a low energy transfer and a long radiation range, resulting in low-level radiation exposure for the patient with optimal imaging condition. In contrast to anatomical imaging like CT or MRI, molecular imaging visualizes tumor molecules and characterizes tumor tissue, function, and biology. This allows not only for disease localization, staging and restaging, but also, and a unique feature of theranostic, the ability to effectively select patients for subsequent TRT based on their chances to have a positive response to therapy[11,12]. Molecular imaging determines whether there is sufficient expression of the molecular target based on tumor uptake compared to normal tissue and background uptake, and therefore whether the patient will benefit from TRT. This principle indicates that treatment with the same compound will be delivering a tumoricidal radiation dose to the cancer cells. TRT is a systemic cytotoxic treatment which is applied either intravenously or orally. The ionizing radiation aims directly at the cancer-specific target and induces deoxyribonucleic acid (DNA) double-strand breaks and subsequently organized cell death through apoptosis. Therefore, choosing the most appropriate radionuclide is key[13].

The higher the linear energy transfer (LET) to the target cell, the higher the damage to the target cell and treatment efficacy. Also, the longer the emission range, which is the tissue penetration range, the larger the perimeter of the irradiated tissue area/treated area (measured in microns up to 2 mm). Preferably, a radionuclide with a relatively long half-life (days to 1-2 weeks) is chosen to prolong the therapeutic effect. The most commonly used radioemitters in the clinic are beta particles like 131I, Lutetium-177 (177Lu), Samarium-153 (153Sm), and Yttrium-90 (90Y). They are characterized by a high energy transfer to the tumor cell and a short radiation emission range, which is favorable to spare surrounding healthy tissue cells. Treatment with alpha particles like Radium-223 (223Ra) has been approved by the US Food and Drug Administration (FDA), others like Actinium-225 (225Ac) are being actively researched in human clinical trials. Compared to beta emitters, they are distinguished by a very high LET and an even shorter path length in the dimension of microns (<100 μm)[14].

Another group of emitters that have been used in the past for theranostics are Auger electron emitters. However, these radionuclides are generally less effective as they provide very low energy electrons that decay by electron capture. The energy is deposited over a very short distance, so they become most effective strictly

intracellularly. Examples of Auger electron emitters are 123I, Indium-111 (111In), Gallium-67 (67Ga), and Technetium-99m (99mTc), which are currently used for SPECT/CT at very low diagnostic doses, but some of them like 123I and 111In have been introduced in clinical trials at high doses for treatment of thyroid diseases and neuroendocrine tumors (NET), respectively[15]. In addition, radionuclides usually have two or more types of emission with different energy peaks. This characteristic makes certain radioisotopes used for therapy to be suitable for non-diagnostic imaging. This non-diagnostic imaging can be of great utility to obtain post-treatment SPECT/CT imaging to confirm molecular targeting of the treatment, rule out pharmacologic interference and stunning. This is usually the case with beta emitters, which tend to have a certain abundance of gamma emission suitable for post-treatment imaging with SPECT/CT. These scans can also be used for dosimetry to determine the absorbed doses of the tumor(s) and healthy tissues.

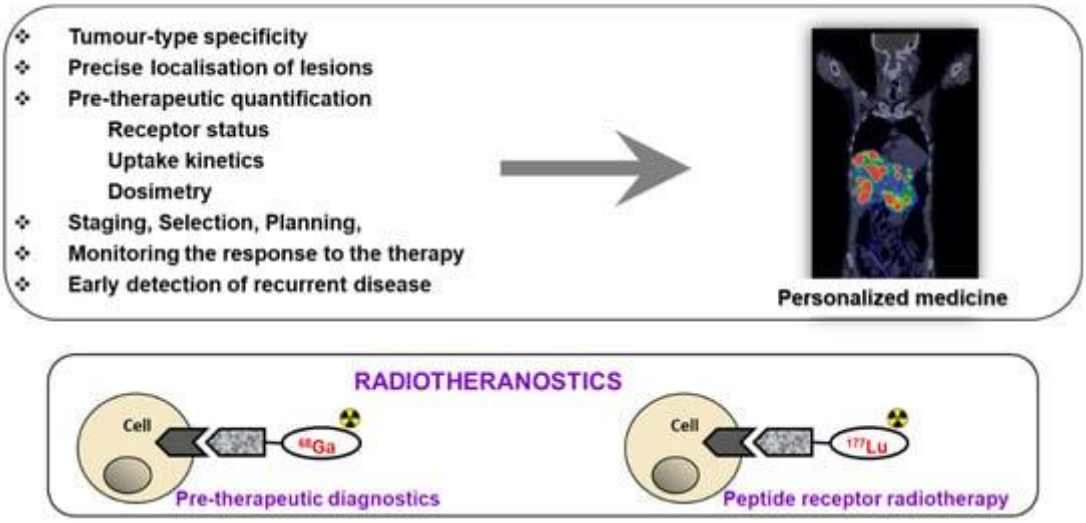

Fig. 1 Radiotheranostics diagnostics and Peptide receptor radiotherapy

Thyroid diseases- Radioiodine Beyond

Thyroid cancer is the most prevalent endocrine malignancy, and the incidence of papillary thyroid carcinoma (PTC) has increased over the past few decades due to improved diagnosis . The American Cancer Society estimates 44,280 new cases of thyroid cancer in 2021 in the United States . Differentiated thyroid cancer (DTC) accounts for the vast majority of thyroid cancers. They arise from follicular epithelial cells and are divided in PTC (85%), follicular thyroid cancer including conventional (5%) and oncocytic (Hürthle cell) carcinomas (5%), poorly differentiated (<3%) and anaplastic thyroid cancer (<3%) .

Radioiodine treatment utilizes the underlying thyroid physiology of using iodide to synthesize thyroid hormones. Iodide is taken up from the blood stream by follicular thyroid cells through the sodium-iodide symporter (NIS) localized in the basolateral membrane. The NIS cotransports two sodium ions along with one iodide ion into the cytosol whereas the sodium gradient serves as driving force. The efflux of iodide across the apical membrane into the follicular lumen is mediated by pendrin channels. Thyroid peroxidase organifies iodide by oxidation and attachment to thyroglobulin. Iodinated thyroglobulin re-enters the follicular cell via endocytosis, undergoes hydrolysis, and the thyroid hormones T3 and T4 are subsequently secreted into the blood stream at the basolateral membrane[16].

Novel targeting ligands and methodologies

Extending the spectrum of radioactively-labelled ligands beyond peptides is both feasible and promising; for instance, the incorporation of radiotheranostics as antibodies will augment the number of druggable targets. Moreover, prospects for advancement exist with tiny chemicals, nanobodies, and customized proteins[17]. In addition to the development of novel targeting ligands, pretargeted radioimmunotherapy may enhance efficacy relative to therapies that do not employ pretargeting. This two-step method involves administering non-radioactive tumor-

targeting antibodies to patients, followed by a delay of 24 to 48 hours to facilitate blood clearance and tumor accumulation, following which a low-molecular weight radioactive agent with a high affinity for the localized antibody is administered[18]. Most pretargeted radioimmunotherapy strategies in preclinical studies have employed antibody–streptavidin conjugates or fusion proteins labeled with 90Y-DOTA biotin.Click-chemistry methodologies in preclinical research have been established for pretargeting in imaging and therapeutic applications[19-20].

Radiotheranostics in Relation to Cancer Stem Cells (CSC)

Researchers have developed numerous approaches to identify and characterize Cancer Stem Cells (CSCs), acknowledging their crucial role in the focused and effective treatment of cancer. The incorporation of monoclonal antibodies (mAbs) into radiotheranostic strategies for targeting cancer stem cells (CSCs) holds significant promise for improving CSC identification and customizing targeted anti-CSC therapy[21]. A theranostic formulation including 68Ga-ventilator and 177Lu-pentixather has been proposed for CXCR4-targeted therapy in certain cancer patients. Nano protein chemokines, a subfamily of cytokines, are released by many stromal and epithelial cells. Al-Ejeh and colleagues investigated the effectiveness of a multifaceted strategy incorporating chemotherapy, peptide receptor radionuclide therapy, and 177Lu-labeled anti-EGFR monoclonal antibodies, aimed at the targeted suppression of Cancer Stem Cells in cases of triple-negative breast carcinoma. Radioimmunotherapy demonstrates remarkable potential in both the elimination of cancer stem cells (CSCs) and the substantial inhibition of tumor growth, as illustrated by the application of 131I-AC133, which effectively targeted colonic CSCs expressing CD133 and significantly impeded neoplastic proliferation in a considerable proportion of cancer cells[22].

Conclusion

Radiotheranostics are radiation-based therapeutic techniques that integrate molecular targeting with optimized radiation dosimetry, and are poised to become a significant component of cancer treatment in nuclear oncology.To actualize the promise of this treatment, interdisciplinary collaboration is essential to address the structural, budgetary, and educational obstacles in establishing therapeutic teams that have the necessary methodological and medical knowledge.

The degree of first clinical success will influence the proliferation of specialized theranostic centers and the quantity of qualified professionals. Collaborative alliances with industry will be crucial for the effective advancement of theranostics.Significant work remains with our existing medications, including the identification of ideal radiomic characteristics to delineate patients most likely to benefit, as well as determining the most effective therapy dosages and frequencies. Given the advancement and exploration of novel therapies including new targets, platforms, and radionuclides, further indications are anticipated in the near future. Logistical, regulatory, and financial obstacles must be addressed; yet, the future appears promising with the ongoing advancement of meticulously constructed prospective clinical trials grounded in robust preclinical and oncological concepts.

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