Radiotheranostics: A Bridge to Personalized Medicine

The road to knowledge is paved by great ideas; using the same target, effective for both diagnosis and treatment, is certainly one of them. The rapid development of radiotheranostics in the last decade has been driven by the availability of radiolabelled agents able to specifically bind molecular targets expressed by diseased cells for diagnostic and/or therapeutic application [1].

The new findings that emerged in the last few years on the applications of radiotheranostics in oncology are supporting the idea that nuclear medicine with injectable radiopharmaceuticals directed against molecular targets could play a relevant role in cancer care and personalized medicine [2].

In this issue of Current radiopharmaceuticals, Mirzaei and colleagues provide a comprehensive insight into the recent advances of radiotheranostic, also highlighting the potential scenario expected in the near future [3].

The path to radiotheranostics has been accelerated by the FDA approval of 177Lu-Dotatate for the treatment of neuroendocrine tumors (NETs). Although NETs are reported as uncommon tumors with an incidence rate of about 5 cases per 1,000,000 [4], their role in the development of radiotheranostics techniques has been essential.

The expression of somatostatin receptors (SSTRs) in about 80-90% of well-differentiated NETs had already suggested the use of functional imaging techniques for the in-vivo detection of SSTRs expressing tumors [5-7]. Moreover, with the increased availability of PET scanners, several authors reported [68Ga]-Dota Peptide PET/CT to be more accurate than a conventional modality, including octreotide-based SPECT imaging [8, 9]. FDA approval for the treatment of NETs came after phase III NETTER-1 trial results showing that treatment of metastatic gastrointestinal (GI) NETs with 177Lu-Dotatate resulted in a significant increment in progression-free survival (PFS) and overall survival (OS) than standard care with cold octreotide [10].

Although new studies are underway on the treatment of NETs with 177Lu-DOTATATE (NETTER-II), a significant increase of treatments is not expected given the low incidence of NETs.

Radiotheranostics has also found application in other human solid tumors, and among these, prostate cancer seems to promise the most interesting results and a more extensive use considering the incidence of this tumor in the male population. Prostate cancer is a disease of increasing worldwide relevance. Global cancer statistics estimates in 2020 report this tumor as the most commonly diagnosed in men, with approximately 1.4 million new cases worldwide (7.3%) and the leading cause of cancer death after lung tumor [11]. Prostate cancer caused 375,304 deaths in 2020, representing 3.8% of the total cancer deaths. Disease incidence is higher in developed than in developing countries and is significantly associated with Human Development Index (HDI) [12].

Prostate cancer often takes years before becoming detectable and continues to grow slowly even after diagnosis. It was recently reported that relative survival of men with prostate cancer at 1, 5, and 10 years after diagnosis was 99%, 97.6%, and 97.2%, respectively [13].

Such long progression times make it possible to identify the most accurate diagnosis and treatment strategies to contrast prostate cancer, thus obtaining complete responses or longer progression time.

Molecular imaging of prostate cancer (PCa) has been initially obtained with PET and [11C] - and [18F]-labelled choline radiopharmaceuticals. The rationale for using choline-based radio compounds in prostate imaging relies on the increased level of phosphorylcholine and phosphatidylcholine turnover observed in prostate cancer cells [14].

Several authors report significant and high sensitivity in the detection of prostate cancer lesions using radiocompounds based on both 18F and 11C radioisotopes over different plasma levels of prostate-specific antigen [15, 16].

PSMA is overexpressed in PCa transmembrane cells and a variety of non-prostatic solid tumors [17]. The growing clinical interest in PSMA as a potential molecular target is based on the enhanced proliferative and migration property of PSMA overexpressing cells [15, 18, 19]. 68Ga-PSMA PET/CT showed a high detection rate (DR) and positive predictive value (PPV) in recurrent PCs staging [20]. Moreover, compared to choline radiolabelled agent, PSMA PET/CT showed a higher detection rate of PCa lesions at low PSA levels (≤ 1 ng/ml) [21].

Given the increased clinical interest in PSMA based radiotheranostics agents, several trials are underway to evaluate the added value of 68Ga-PSMA PET/CT imaging compared to conventional imaging modalities. Similarly, other trials are under-
way to evaluate the utility, benefits and limitations of 177Lu-PSMA in PCa therapy. A detailed list of active trials is reported by Jadvar H [22].

A strategy potentially useful in the development of more effective radiotheranostics agents arises from engineered antibodies fragments called "nanobodies." Nanobodies could provide properties such as specificity, stability, thermotolerance and reduced immunogenicity useful for radiotheranostic agents to be used in diagnostics and therapy [23].

Although the majority of studies focused on 68Ga labeled agents, other studies are underway to evaluate the feasibility of radiotheranostics agents based on isotopes, such as fluorine (F18), copper (64Cu), iodine (I124), and scandium (SC44), for targeted imaging as well as iodine (I131) and actinium (225Ac) for treatment.

In preliminary findings, the biodistribution of 68Ga and 64Cu-labeled PSMA in a population of 30 PCa patients was found to be not significantly different [24]. Study results document only a difference among radiotracers distribution due to renal and biliary excretion for 68Ga and 64Cu-PSMA, respectively [24].

However, there is a lack of registered clinical trials aimed at evaluating the advantages and limitations of different radio compounds. Despite the exponential growth of translational and cohort studies on radiotheranostics in oncology, the need for well-designed trials providing level I evidence that are able to drive clinical management will be the key point for future radiotheranostics development.

In conclusion, pieces of evidence published so far suggest a rapidly evolving scenario of substantial changes in cancer diagnosis and treatment. In a presumably medium-term time horizon, the growing body of knowledge will help define the role of radiotheranostics in the context of targeted medicine.

The role and clinical impact definition of radiotheranostics in patients with prostate cancer will be the next step of nuclear medicine along the path of personalized medicine.

REFERENCES


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