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Malignant Neuroendocrine Tumors and Radioisotope Research: A Vision of Innovative Theurapeutic Methods and Rational Development of Targeted Therapy

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Abstract

Neuroendocrine tumors (NETs) are a group of uncommon tumors that start in your neuroendocrine cells. These cells combine the traits of nerve cells and hormone-producing cells. Most neuroendocrine tumors are malignant .There are several types of neuroendocrine tumors with symptoms that are easy to mistake for other less serious conditions. The characteristics of NETs including how aggressive (fast-growing) they are, the symptoms they cause and what treatments work best — vary significantly based on the tumor.

Traditional therapeutic approaches such as chemotherapy and radiation therapy have burdened cancer patients with onerous physical and psychological challenges. Encouragingly, the landscape of tumor treatment has undergone a comprehensive and remarkable transformation. Emerging as fervently pursued modalities are small molecule targeted agents, antibody-drug conjugates (ADCs), cell-based therapies, and gene therapy.

Key words: Radionuclide Theraphy, NET.

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Introduction:

Neuroendocrine neoplasms are a heterogeneous group of malignant tumors, their neuronal properties being determined by the identification of DCGS4, which is similar to DCG in serotonergic neurons. The endocrine properties are related to the synthesis and secretion of monoamines.

The neuroendocrine (NE) system includes endocrine glands, such as the pituitary, the parathyroids, and the NE adrenal, as well as endocrine islet tissue embedded within glandular tissue (thyroid or pancreatic) and scattered cells in the exocrine parenchyma, such as endocrine cells of the digestive and respiratory tracts, which belong to what is known as the diffuse endocrine system. The GI tract (62-67%) and lungs (22-27%) are the most common primary tumor sites. **[2]**

NETs express several growth factors and cognate tyrosine kinase receptors (RTK), including VEGF, PDGF, IGF1, bFGF and transforming growth factor (TGF)-α and -β. These different growth factors trigger multiple, and often overlapping, intracellular signals via distinct mechanisms. Among them the activation of the phosphatidyl inositide 3 kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) pathway, driven by a number of RTKs, has a central role in survival and/or proliferation of NET cells **[1].**

Differentiation allows us to identify two distinct prognostic groups: well differentiated (WD) and poorly differentiated (PD) neoplasms . Although PD group is biologically aggressive and usually followed by an unfavorable clinical course, the WD group comprises tumors that can be completely cured or can permit long-term survival even with relapse or metastasis, but it has to be sayed that all aspects are chatacteristic to the organ of origin.

As first-line treatment, localized tumors or NETs showing only regional spread, require surgery with either radical or cytoreductive purpose, probably able to relieve symptoms even of metastatic and/or high-grade NETs. In the case of metastatic NETs (about 85% of all NETs) , medical treatment is recommended and very much needed.**[1]**

Histology:

Well-differentiated NET cells produce secretory granules with intense immune expression of neuroendocrine granules such as chromogranin A (CgA) and synaptophysin (Syn). In contrast, NECs demonstrate a solid "sheetlike" proliferation of tumor cells with irregular nuclei, high mitotic features, and less cytoplasmic secretory granules.

Up to 40% of NECs contain elements of non-neuroendocrine histology; it should be said that, the neuroendocrine component has to exceed 30% for the tumor to be called an NEC; otherwise, it is classified as a mixed adenoneuroendocrine carcinoma.

Classification:

Year 2000, gastroenteropancreatic (GEP) classification by WHO:

1. Well-differentiated neuroendocrine tumor with probably benign behavior

2. Well-differentiated neuroendocrine tumor with uncertain behavior

3. Poorly differentiated neuroendocrine carcinoma with high-grade malignant behavior

In 2010, the latest version of the WHO classification appeared, which redefined the entire group of tumors as NENs. GI NENs were subdivided according to their mitotic count or Ki67 index, associated with cellular proliferation. It is important to empesize that (as with many tumor types) histologic grade

does not always correlate with clinical behavior. The majority of NENs are sporadic, but hereditary syndromes that include multiple endocrine neoplasia type 1 (MEN-1), MEN-2, von Hippel–Lindau (VHL) syndrome, neurofibromatosis, and tuberous sclerosis.

NETs are also highly vascularized, which makes inhibition of vascular endothelial growth factor (VEGF) signaling a relevant treatment option. The VHL gene is associated with the regulation of hypoxia-inducible factor (HIF); increased expression of HIF targets, such as VEGF, has been linked to the development of pancreatic NETs.

Mutational analysis of pulmonary NENs has also demonstrated multiple genetic anumalies, such as FGF2 mutations in large-cell NEC; KIT, PTEN, HNF1A, and SMO alterations in atypical carcinomas; JAK3, NRAS, RB1, and VHL1 mutations in SCLC; and SMAD4 mutations in typical carcinoids.

NENs are usually asymptomatic and are discovered incidentally. Appendiceal NENs: Usually do not degenerate into carcinoid, are common in premenopausal women, and present with hypogastric pain. Differential diagnosis with gynecological diseases is necessary**[5]**

Tumor Markers:

Besides CgA and 5-HIAA, NENs are known to produce a plethora of bioactive amines and peptides such as 5-hydroxytryptamine, 5-hydroxytryptophan, serotonin, insulin, gastrin, glucagon, somatostatin, vasoactive intestinal peptide, growth hormone, adrenocorticotropic hormone, melanocyte-stimulating hormone, pancreatic polypeptide, calcitonin, substance P, pancreastatin, etc., resulting in relatively uncommon but unique clinical syndromes.

In addition to the general oncological treatment regimen, NENs require the involvement of radiologists and narrow-specialty physicians. The basis of treatment is Surgical treatment, since most NETs are identified in the advanced metastatic stage of the disease[2].

Radiopharmaceuticals play essential role for targeted treatments and diagnostic imaging. These carefully crafted chemicals provide non-invasive insights into cellular molecular processes by fusing radioisotopes with physiologically active substances. These medications go beyond conventional medications. This opens a new era of customized medicine by enabling medical professionals to tailor therapies to the particular needs of each patient, increasing efficacy and minimizing adverse effects. The combination of medications and radioisotopes has also produced innovative imaging methods that reveal the processes going on within our bodies.

A ligand, such as an antibody, peptide, or small molecule, is strategically linked to a radioactive molecule, such as a radioisotope, in a process known as active targeting. This technique is intended to increase therapeutic efficacy and reduce the toxicity of radiopharmaceuticals by specifically delivering radiation treatment to cancer cells that express particular receptors. The somatostatin receptor overexpressed in neuroendocrine tumors is the target of Lutetium-177 dotatate (Lutathera), one of several effective instances of radiopharmaceuticals employing active targeting. A phase III clinical trial that was approved by the FDA in 2018 for the treatment of gastroenteropancreatic neuroendocrine tumors showed better overall response rates and progression-free survival than standard therapy. Radium-223 dichloride (Xofigo) is another example; it preferentially accumulates in bone metastases and attacks the bone matrix. Using Bexxar, iodine-131 tositumomab targets the CD20 antigen expressed on B-cell lymphomas and B cells. These illustrations demonstrate how active targeting can be used to target certain cancer cells with radiation therapy, which is a major breakthrough in precision medicine.

A cutting-edge method for drug delivery, stimulus-responsive release systems enable the regulated release of active pharmaceutical ingredients (API) in response to particular stimuli or circumstances, such as light, magnetic fields, pH, temperature, or redox. For the targeted delivery of radiopharmaceuticals, a variety of stimuli have been investigated. For example, liposomes, micelles, or polymers are examples of pH-sensitive nanocarriers that can selectively release radiopharmaceuticals by taking advantage of the acidic environment found in tumors. In response to hyperthermia, temperature-sensitive materials—like

thermosensitive polymers or liposomes improve nanocarrier permeability and trigger the release of radiopharmaceuticals. When tumor cells produce more reactive oxygen species (ROS), redox-sensitive nanocarriers release their payload. Remote control of the release is made possible by light-sensitive nanocarriers, such as photoresponsive polymers or liposomes of radiopharmaceuticals through the application of particular light wavelengths, intensities, or durations.

Case studies using radiopharmaceuticals show a novel approach to treating bone metastases. Striking examples emerge where targeted radiopharmaceutical therapies, such as strontium-89 chloride or samarium-153 lexidronam, deliver focused radiation to osteoblastic or osteolytic lesions, offering relief from pain and promoting skeletal stability. Examples show how combining radiopharmaceutical treatments with external beam radiation, systemic medications, or surgery can have a synergistic effect, increasing the range of therapy options available to patients with bone metastases.

There are important factors and tactics to take into account when ensuring the safety of individuals handling radiopharmaceuticals. To maintain the integrity of radiopharmaceutical preparation the strict quality control procedures are essential. These procedures involve personnel, materials, and ongoing result review.

Radiotheranostics:

PRRT (also called radioligand therapy) for NET has become a paragon of modern theranostics. PRRT holds a favorable toxicity profile, and it is associated with a prolonged time to progression, reduction of symptoms, and improved patients' quality of life **[2].**

Radiotheranostics, a worldwide expanding clinical procedure in oncology, combines medical nuclear imaging with targeted radionuclide therapy. It involves the systemic intravenous administration of a radiopharmaceutical. The radiopharmaceutical consists out of a vector with high affinity and selectivity for the target tissue and either diagnostic or therapeutic radionuclide . Single photon emission computed tomography (SPECT) and positron emission tomography (PET) are the two molecular imaging techniques that are available in nuclear medicine. Theranostics is one of the most promising applications of precision medicine and a major emerging branch of nuclear medicine. Its concept consists of targeting disease-specific features to detect and treat tumor lesions : at first, a radiopharmaceutical is marked with a positron-emitting radionuclide and used for positron emission tomography (PET) lesion detection, then the same compound is labeled with a different radionuclide, emitting a cytotoxic radiation (e.g., beta-minus or alpha) for target treatment **[3].**

Within the field of radiotheranostics, targeted alpha therapy (TAT) aims to harness the high cytotoxic payload of alpha-emitting radionuclides to treat cancer based on unique tumor cell targets. Alpha particles have the desired short penetration range within the tissue which allows focused endogenous radiation of a restricted region of interest, with minimal damage to surrounding tissue **[2].**

PRRT is an effective treatment for well differentiated NET, already included in EANM/SNMMI, ESMO, and ENETS guidelines. To optimize the therapeutic index, many studies are on-going investigating delivery of PRRT at earlier time-points in the natural history of the disease, comparison with other approved drugs, combination with chemo/target therapy, PRRT re-treatment, different administering PRRT protocols (cycles number and dose/cycle), use and combination of different radionuclide therapies (beta-minus and alpha emitters), and development of new theranostic pairs

PRRT with [177Lu][Lu-DOTA0-Tyr3]octreotate ([177Lu]Lu-DOTATATE) was approved by the European Medicines Agency (EMA) in 2017 and Food and Drug Administration (FDA) in 2018 . According to EMA, [177Lu]Lu-DOTATATE is approved for unresectable or metastatic, progressive, well-differentiated (G1 and G2), SST-positive GEP NET in adults . Patients' eligibility for PRRT requires SST PET/CT positivity (uptake considered significant if at least above the liver parenchyma) . PRRT is included in ESMO and ENETS clinical guidelines. finally, the most recent studies confirm the knowledge received so far regarding PRRT safety and efficacy and demonstrate comparable outcome

data, indicating that this therapeutic option is based on solid evidence.

Although PRRT was reported as a safe therapeutic option in NET patients with up to 50% liver involvement a recent study has shown the risk of radiation-induced hepatotoxicity in patients with more than 75% of liver involved.

PET functional imaging may detect even non-enlarged nodes or bone lesions (either millimetric or without corresponding morphological changes on CT) when presenting high SST expression. In addition, mere changes in tumor dimension may lead to unclear interpretation. For example, a stable lesion may mask intralesional de-differentiation while a decrease in tumor volume after chemotherapy could subtend a cyto-reductive effect on the most aggressive components without a significant effect on SST-expressing cells. In addition, an initial increase in tumor volume may be related to inflammatory mechanisms (i.e., pseudoprogression), involving up to 10% of patients after PRRT.

In the last decade, SST-PET/CT has almost completely replaced somatostatin receptor scintigraphy as a tool to select patients for PRRT, due mostly to its higher accuracy and quantification.

As for all radiation treatments, the issues of radiosensitivity and radioresistance are to be considerated. chemotherapy can work both with a direct cytotoxic effect and as a radiosensitizer, contrasting DNA repair and cell proliferation; this rationale led researchers to analyze the combination of various cytotoxic treatments with PRRT, obtaining promising results on the outcome and safety profile.

Another approach to maximize PRRT efficacy is to overcomplicate the neovascularization characterized for advanced tumors (including NEN), which tends to interupt drug delivery, due to the fragile and disorganized blood vessels. Sunitinib is a multi tyrosin kinase inhibitor with an anti-proliferative and anti-angiogenic action, only approved for the treatment of advanced pancreatic NET on the basis of the SUNNET phase III trial.

The therapeutic options available to date for advanced NEN can have effect on different molecular pathways in the absence of clear prioritization sequencing protocols. **[3]**

Somatostatin receptor radionuclide therapy and NET

Both ENETS (The European Neuroendocrine Tumor Society) and NANETS (The North American Neuroendocrine Tumor Society) recommend that patients who are candidates for PRRT should have SSTR positive metastatic or inoperable NETs, have an adequate hematologic reserve, be able of an adequate performance, and show either objective or clinical progression of disease/symptoms.

SSTR expression is most commonly messured by the Krenning score, which studies tumor SSTR expression on somatostatin receptor imaging (SRI) relative to healthy organs. More recently, gallium-68 (68Ga)-based somatostatin receptor imaging (i.e. 68Ga-DOTATATE) has demonstrated markedly higher sensitivity and improved image resolution. PRRT is considered appropriate for patients having tumors with a Krenning's score of at least 2 (equivalent to the liver) on OctreoScan or SSTR expression higher than healthy liver on 68Ga-based SSTR PET. All lesions above the sensitivity threshold for the scan (typically greater than approximately 8 mm in diameter) must express sufficient uptake.

the selection of patients, which imaging studies and biomarkers are most useful pretreatment and on-treatment, and choice of radionuclide (177Lu alone or in combination with 90Y). Novel PRRT agents utilizing α-emitters and SSTR antagonists are in development and offer theoretical advantages over 177Lu-DOTATATE. Combination strategies to increase the potency of PRRT are also in development including ongoing trials combining the treatment with cytotoxic chemotherapy (CAPTEM and fluorouracil), radiation sensitizers (triapine) and PARP inhibitors. **[4]**

Conclusion:

Modern nanotechnology combined with radiopharmaceutical chemistry has the potential to revolutionize treatment efficacy and diagnostic precision.

As researchers don’t know what causes NETs, there’s nothing you can do to prevent them. Still, you can understand potential risk factors, like having an inherited condition like multiple endocrine neoplasia (MEN). Therefore, innovative therapeutic approaches to address risk factors, remission, and treatment support are becoming increasingly relevant for the global healthcare system.

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