Cholecystokinin-2 Receptor

Subjects: Radiology, Nuclear Medicine & Medical Imaging

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The cholecystokinin-2 receptor (CCK2R) is a promising target for theranostic use in nuclear medicine, and has been in the focus of the radiopharmaceutical development over the last twenty years. The expression of this receptor at high incidence and density has been proven mainly for medullary thyroid carcinoma (MTC) and small cell lung cancer (SCLC). Furthermore, CCK2R expression has been confirmed for gastrointestinal stromal tumors, astrocytomas and stromal ovarian cancers. In addition, CCK2R targeting might be of additive value for gastroenteropancreatic and bronchopulmonary neuroendocrine tumors, especially insulinomas, vipomas, as well as bronchial and ileal carcinoids. Most of the clinical experience with CCK2R targeting radiopharmaceuticals has been gained for patients with advanced MTC. Therefore, the diagnostic and therapeutic potential of CCK2R targeting is documented mainly for this patient group.

cholecystokinin-2 receptor | tumor targeting | molecular imaging | targeted radiotherapy

1. Introduction

The development of radiolabeled cholecystokinin-2 receptor (CCK2R) targeting peptide analogs was initiated in the late 1990s. Several pioneers laid the foundation for this new diagnostic and therapeutic approach. Strong CCK2R expression, especially in medullary thyroid carcinoma (MTC) and its metastases, was demonstrated by the group of Prof. Jean Claude Reubi [1]. First scintigraphic visualization of tumor lesions in a patient with metastasised MTC using 131I-labeled gastrin was undertaken by Thomas Behr in 1998 [2]. In this team, Martin Béhé developed the first 111In-labeled gastrin derivatives with selective affinity for CCK2R [2][3]. The research group around Marion de Jong worked on non-sulphated cholecystokinin analogs. By increasing specificity for CCK2R over CCK1R, reduced uptake in normal tissue expressing CCK1R was achieved [4]. Soon thereafter, additional research groups across Europe directed their attention to the preclinical development of peptide-based CCK2R targeting probes.

Since the very beginning, the difficulties in the development of clinically useful radiolabeled CCK2R targeting peptide analogs became clear. These were related either to high kidney uptake, leading to nephrotoxicity during therapeutic application, or low enzymatic stability, limiting the tumor targeting properties [5][6]. The clinical comparison of three different 111In- and 99m Tc-labeled derivatives of human minigastrin (MG) and cholecystokinin-8 demonstrated the need for further radiopharmaceutical development to enable CCK2R-based peptide receptor radionuclide therapy (PRRT) [7]. A small, but well networked radiopharmaceutical community accelerated the radiopharmaceutical development. Within the COST (European Cooperation in Science and Technology) Action BM0607 on Targeted Radionuclide Therapy, twelve different CCK2R targeting peptide analogs

were preclinically evaluated, with the major aim of finding a promising new candidate for PRRT [8][9][10]. These joint efforts triggered further clinical studies and gave new directions to the ongoing preclinical research.

2. Tumor Imaging with Radiolabeled Gastrin Analogs

Survival of cancer patients largely depends on early localisation of the disease and accurate assessment of its extent, as well as early detection of locoregional recurrence and distant metastases. Therefore, there is a need to develop imaging diagnostic strategies tailored to the specific, possibly unique, features of the tumor. Radiolabeled gastrin analogs may be applied in the visualization of various forms of CCK2R-expressing neoplasms in order to determine the range of the surgery and positioning of locoregional and systemic therapies in a personalised approach to current diagnostic and therapeutic algorithms in these tumors.

Serum calcitonin (Ct) concentration is recognized as an accurate estimation of tumor burden in MTC patients [11][12]. Repeatedly detected Ct concentration above 10 pg/mL suggests persistence of the disease [13]. However, due to the lack of sensitive imaging tools to detect small MTC foci, basal Ct of 150 pg/mL is still a recommended threshold value for imaging procedures, as set by scientific societies. However, the wider use of PET/CT imaging with new tracers, resulting in higher sensitivity, may change this recommendation [11][13][14][15][16].

Current clinical guidelines of different scientific societies recommend the use of various radiopharmaceuticals for MTC imaging. The clinical practice guidelines of the National Comprehensive Cancer Network recommend conservative surveillance with repeated measurement of the serum markers, as well as additional imaging studies, including also [^{18}F]FDG and [^{68}Ga]Ga-DOTA-TATE PET/CT, in MTC patients with Ct concentrations above 150 pg/mL and negative conventional imaging [14]. The European Association of Nuclear Medicine (EANM) [17] and the European Society for Medical Oncology (ESMO) [13] also recognize [^{18}F]FDOPA PET/CT as very useful in clinical practice. According to the ESMO guidelines, work-up for distant metastases with [^{18}F]FDOPA PET/CT should be performed if Ct concentrations exceed 500 pg/mL, or when clinical findings are suspicious [13]. In a meta-analysis performed by Lee et al., [^{18}F]FDOPA PET was found to have the highest detection rate of recurrent MTC among five PET radiopharmaceuticals: [^{18}F]FDG, [^{18}F]FDOPA, ^{68}Ga-labeled somatostatin analogs, 3-O-methyl-6-[^{18}F]fluoro-DOPA, and [^{11}C]methionine [18].

Despite the promising preclinical data presented above, there are only a few clinical studies or case reports on the use of radiolabeled gastrin analogs in diagnostic imaging in MTC patients to support their efficacy. Nevertheless, based on the current clinical research, radiopharmaceuticals targeting CCK2R should be considered as sensitive and highly specific biomarkers. However, in order to obtain sufficient evidence and to establish the role of radiolabeled CCK2R analogs for imaging in the diagnostic and therapeutic algorithm in MTC patients, it is necessary to obtain more clinical data. This is hindered by the rarity of these tumors, resulting in usually small numbers of patients included in the individual studies.

A limited number of radiolabeled CCK2R-targeting peptide analogs that have been tested in pilot clinical trials in humans achieved receptor targeting, as well as safety, tolerability and, most importantly, tumor-to-background

ratios sufficient for potential clinical use. A phase I clinical trial using the novel minigastrin analog [^{111}In]In-CP04 for personalized diagnosis and therapy in patients with progressive or metastatic MTC (GRAN-T-MTC; ClinicalTrials.gov (accessed on 22 September 2021): NCT03246659) was conducted in the framework of the international ERA-NET on Translational Cancer Research (TRANSCAN; FP7) [19]. For the purposes of this trial, the peptide analog CP04 was selected because of its favorable pharmacokinetic properties (high metabolic stability and receptor affinity, high and persistent tumor uptake against low kidney retention) among several gastrin analogs evaluated in comparative studies performed within the COST Action BM0607 [8][9][10][20].

The primary objectives were to determine the safety of the intravenous administration, the biodistribution and dosimetry of [^{111}In]In-CP04 in cancer and normal tissues and critical organs, as well as the ability of visualization of MTC lesions. Safe use of the tested compound in humans was confirmed, although there was a marked increase in Ct and procalcitonin concentrations in the blood after tracer injection in some cases of far advanced MTC. In all patients, [^{111}In]In-CP04 uptake was found in MTC lesions regardless of the peptide dose injected (10 or 50 µg), mainly in cervical and mediastinal lymph nodes and liver metastases. In two patients, detection of tumor lesions not identified in CT and MRI, was achieved (cervical lymph nodes metastases were confirmed by histopathology). Infusion of the gelatin-based plasma expander Gelofusine reduced the radiation dose to the kidneys by 53%. Pharmacokinetic data of [^{111}In]In-CP04 were also used for the estimation of the radiation dose that would have been absorbed by the tumor lesions if CP04 was labeled with lutetium-177 [21][22]. In **Figure 1**, an example of SPECT/CT imaging using [^{111}In]In-CP04 in a female patient with advanced MTC is given, showing different lesions in the neck region. The details of the final analyses of the clinical study will be published shortly.

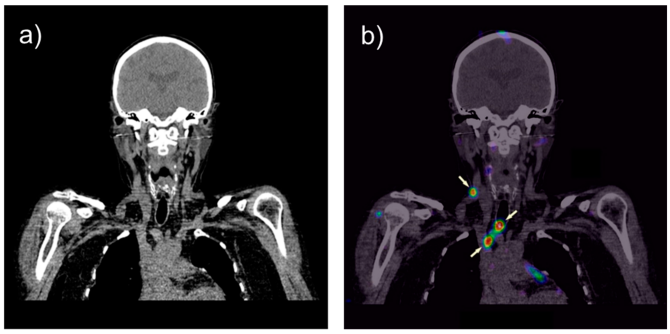

Figure 1. CT (**a**) and fused [^{111}In]In-CP04 SPECT/CT (**b**) images in coronar orientation. Neck lymph node metastases and tumor infiltration around the tracheotomy tube (arrows) in a female patient with MTC are visible; images performed 24 h after injection of 210 MBq (50 µg peptide). Scan was performed within GRAN-T-MTC (ERA-NET on Translational Cancer Research (TRANSCAN), First Joint Transnational Call (JTC 2011) on: “Validation of biomarkers for personalised cancer medicine”, funded by the European Commission under the Seventh Framework Programme (FP7) with the following national co-found institutions: Ministry of Health (MoH), Italy, National Centre for Research and Development (NCBiR), Poland, Federal Ministry of Education and Research (BMBF), Germany, Austrian Science Fund (FWF, Project No. I1224-B19), Austria, Ministry of Higher Education, Science and Technology (MHEST), Slovenia, and General Secretariat for Research and Technology, Ministry of Education, Life Long Learning and Religious Affairs (GSRT), Greece.

^{68}Ga-labeled CCK2R-targeting peptide probes for PET imaging in MTC will probably be increasingly used in clinical practice, however, to date the clinical data are sparse [23]. In 2016, Kunikowska et al. used a SSTR and a CCK2R targeting peptide analog, both radiolabeled with gallium-68, to visualize primary MTC in the right thyroid lobe of a male patient obtaining good tumor visulization with both radiopeptides [24]. Using the CCK2R targeting peptide, a lower uptake in liver and kidneys as compared to ^{68}Ga-SSTR PET was seen, together with physiological uptake in the stomach.

The first experience with the novel ^{68}Ga-labeled minigastrin analog [^{68}Ga]Ga-DOTA-MGS5 in comparison to [^{18}F]FDOPA was described by Uprimny et al. in 2021 in a female patient with advanced MTC. PET/CT with [^{68}Ga]Ga-DOTA-MGS5 vs. [^{18}F]FDOPA showed less cervical lymph node and bone metastases with lower SUV values (lymph nodes 1 vs. 2, SUVmax 3.4 and 2.6 (1/2 h p.i.) vs. 11.7; bone metastasis 1 vs. 3, SUVmax 1.6 and 2.3 (1/2 h p.i.) vs. 4.0). However, [^{68}Ga]Ga-DOTA-MGS5 allowed a better discrimination of liver lesions (SUVmax 6.4 and 8.3 (1/2 h p.i.) vs. 3.73), three additional metastases were found, and physiological liver activity was lower resulting in higher tumor/non-tumor ratios [25]. In **Figure 2** PET/CT imaging with [^{68}Ga]Ga-DOTA-MGS5 PET/CT in a male patient with advanced MTC is presented, showing several liver lesions.

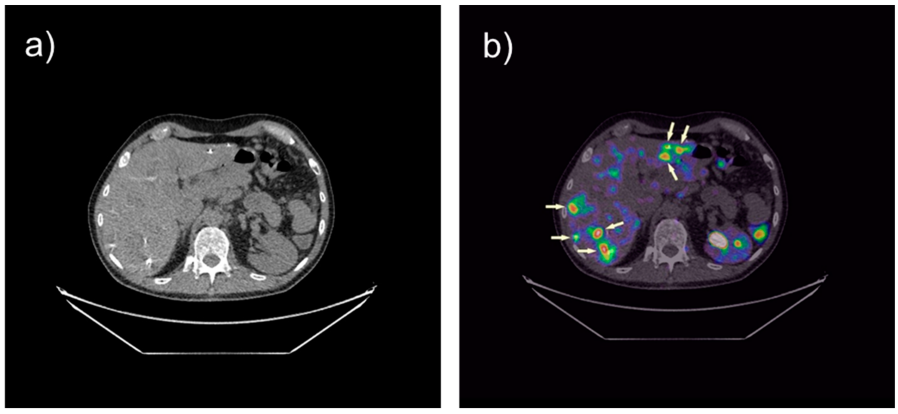

Figure 2. CT (**a**) and fused [^{68}Ga]Ga-DOTA-MGS5 PET/CT (**b**) images in transverse orientation. Multiple liver metastasis (arrows) in a male patient with advanced MTC are visible; images performed 4 h after injection of 165 MBq (<50 µg peptide); courtesy of Prof. Alicja Hubalewska-Dydejczyk.

Recent research on diagnostic imaging with radiolabeled CCK2R-targeting peptide analogs revealed the potential usefulness of these compounds in the management of MTC patients. CCK2R imaging may be preferable to SSTR imaging, especially in MTC patients with low or missing SSTR expression [26][2] and may thus be considered in the earlier stages of diagnostic schemes to optimize the procedures with a more effective strategy, allowing for radical surgery in a larger proportion of patients in order to improve survival. The accurate evaluation of the CCK2R status in individual tumor foci may be of special importance in terms of radionuclide therapy planning. Furthermore, the possibility of assessing CCK2R expression by radiolabeled MG analogs in addition to identifying the genetic profile of the tumors would help to stratify the risk of an unfavorable course of the disease with higher precision in near future. It is known that the different biological behavior of the mutations is responsible for differences in the latency

period and aggressiveness of MTC [27][28][29]. Therefore, an individual genomic/proteomic MTC pattern might drive the choice of functional imaging planning with different available radiopharmaceuticals [30].

3. Tumor Therapy with Radiolabeled Gastrin Analogs

CCK2R is also an interesting target for PRRT. Among tumors expressing CCK2R, MTC is of special interest because of its high receptor incidence in more than 90% of MTC [31] and, on the other hand, the limited therapy options in patients with advanced stages of MTC. Standard therapy of MTC consists in total thyroidectomy and compartment-oriented lymph node dissection, which is the only chance to achieve cure. Patients with postoperative normalisation of the tumor marker calcitonin can be considered “biochemically cured” and have a favorable prognosis [13]. However, in roughly 10% of all patients, distant metastases are present already at the time of diagnosis, and are discovered in further 19–38% of patients during follow-up [13]. Furthermore, initial postoperative biochemical cure is very unlikely in patients with >10 lymph node metastases, and the chances to achieve a long-term biochemical cure are only realistic in patients with very low numbers of positive nodes [16][32]. Until several years ago, when the multikinase inhibitors cabozantinib and vandetanib were introduced as first-line systemic therapy for MTC, systemic treatment options for MTC patients were very limited, since chemotherapy has historically yielded poor results and MTC lacks uptake of radioiodine [13][16]. For tumors harbouring “rearranged during transfection” (RET) mutations, the situation recently improved further with the approval of selective inhibitors of the RET-oncogene, showing higher response rates combined with less side effects [33]. However, the systemic therapies currently approved for MTC have not been shown to improve overall survival yet, and evidence-based guidance on when to start these therapies in patients is still lacking [13]. Therefore, the need for further, effective systemic therapies remains.

MTC was chosen for the first and to date the only published treatment (phase I) study with the CCK2R agonist [^{90}Y]Y-DTPA-MG0 [5]. Eight patients with advanced and rapidly progressing metastatic MTC received up to 1.85 GBq/m^2 body surface, resulting in partial remission (n = 2), stable disease (n = 4) and progressive disease (n = 2) within a follow-up period of 12-36 months. Unfortunately, high hematologic and renal toxicity prevented further trials with this compound. In the course of the following years, further development resulted in MG analogs with improved biodistribution. One of these, [^{177}Lu]Lu-PP-F11N, was chosen for a clinical phase 0 trial as a proof of principle study (ClinicalTrials.gov (accessed on 22 September 2021): NCT02088645) [34]. This compound showed a promising biodistribution with specific uptake in MTC. Dosimetry after infusion of 1 GBq of [^{177}Lu]Lu-PP-F11N revealed radiation doses to MTC lesions sufficient for therapy, combined with low radiation doses absorbed in kidneys and bone marrow. The highest radiation doses were seen in the stomach, which would most likely be the dose-limiting organ. The administration of Gelofusine revealed no significant effect on the already low dose absorbed by the kidneys.

The acute toxicity of [^{177}Lu]Lu-PP-F11N was low with self-limiting adverse events not higher than grade 1, according to Common Terminology Criteria for Adverse Events version 4.03 (CTCAE). Based on the dosimetric calculations, it was stated that fractionated therapy with 50 GBq [^{177}Lu]Lu-PP-F11N should be possible without surpassing maximum tolerated doses of risk organs. In consequence, a phase 1 dose escalation study was

initiated (ClinicalTrials.gov (accessed on 22 September 2021): NCT02088645). Within this trial, the first planned escalation cohort (n = 3) received 3 × 6 GBq without dose limiting toxicity or other toxicity higher than grade 2, according to CTCAE [35]. In all patients, at least a temporary reduction of tumor markers occurred after therapy. In **Figure 3**, an exemplary SPECT/CT image of a patient with hepatic MTC metastases is given, showing specific uptake of [^{177}Lu]Lu-PP-F11N in the liver lesions together with physiological uptake in the stomach. Therefore, the study continued with the next dose escalation step (4 × 8 GBq).

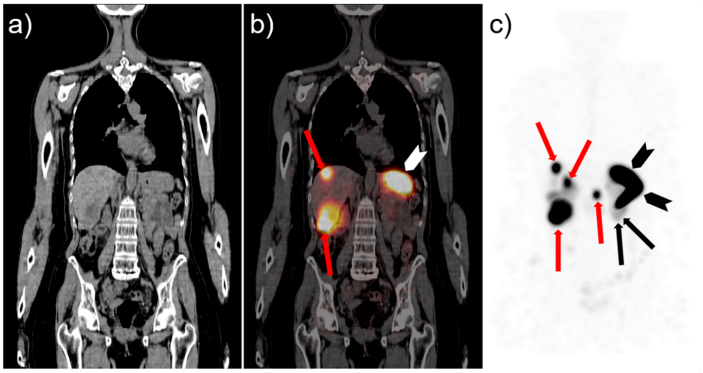

Figure 3. CT (**a**) and fused [^{177}Lu]Lu-PP-F11N SPECT/CT (**b**) images in coronal orientation. Corresponding maximum intensity projection image of SPECT data (**c**). Images 72 h after infusion of 6.3 GBq (<100 µg peptide) in a female patient with hepatic MTC metastases demonstrates strong uptake of the radiopharmaceutical in hepatic metastases and stomach. Red arrows: Liver metastases; white and black arrowheads: stomach; black arrows: Kidney; courtesy of Dr. Christof Rottenburger.

As the clinical evaluation of CCK2R-targeted therapies has only started recently and to date has achieved only preliminary results, this approach is yet to be mentioned in any guidelines for the treatment of MTC. The American Thyroid Association Guidelines recommend the consideration of two approaches of therapy with radiolabeled tracers in selected patients with MTC: SSTR-targeted PRRT and pretargeted anti-CEA radioimmunotherapy [16]. Both strategies could be interesting alternatives of targeted radiotherapy, especially in patients with poor CCK2R expression of tumors [36][37].

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