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EDITORIAL

The LUTIA trial: a small step for PRRT, a giant leap for intra-arterial radionuclide therapy trial methodology

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Targeted radionuclide therapy (RNT) has taken a prominent place in the treatment of neuroendocrine tumors (NETs) and prostate cancer in the last decade [1, 2]. Beta-emitting radiopharmaceuticals targeting specific proteins overexpressed by tumor cells allow precision irradiation of malignant lesions with low-dose irradiation of normal organs. Despite having a profound impact on important endpoints such as symptom control, quality of life, progression-free survival, and overall survival, these therapies are not curative and hence further optimization is warranted. Many strategies are currently being investigated, ranging from combination therapy with radiosensitizers or immune system modulators, changes in vector molecules, novel radionuclides (including alpha- and Auger-emitters), and dosimetry-based therapy personalization [3].

For peptide receptor radionuclide therapy (PRRT) targeting the somatostatin receptor (SSTR), one optimization strategy of interest consists of selective injection of the radiopharmaceutical to the organ with the highest tumor load and the largest prognostic impact. In NET patients treated with PRRT this is very often the liver [4]. Injection into the hepatic artery of a wide range of anti-tumoral agents has been studied and radioactive microsphere treatment has become a standard treatment modality in primary and metastatic liver tumors (called selective internal radiation treatment or radioembolization), familiarizing the nuclear medicine and interventional radiology (IR) team with this treatment route [5]. The main interest of intra-hepatic artery injection is the first pass effect: by assuring that 100% of the injected activity passes through the liver, a higher uptake and hence absorbed dose could be reached in principle. Encouraging preliminary results have been reported using this strategy, both using diagnostic PET agents in proof-of-principle studies and using therapeutic radiopharmaceuticals, demonstrating higher uptake values after intra-arterial (IA) vs. intravenous (IV) injection. Advantages of this strategy include first-pass mediated increased uptake and a more rapid reaching of peak or plateau values in the time-activity curve, which can be of great interest in treatment with short-lived radionuclides (e.g., bismuth-213, half-life 45.6 min) [6]. Disadvantages include the work load for the IR team and use of the IR suite and resulting costs, IA access-related discomfort and adverse events (hematoma, pseudo-aneurysm, pain, etc.), increased radioprotection measures in the IR suite, need for bladder catheter to prevent contamination with the urinary excreted radiopharmaceutical, increased radiation dose to hospital personnel, and increased hospital contamination risk. Given these potential drawbacks, solid evidence should be available to support this treatment strategy before widespread adoption in clinical practice.

The publication by Ebbers et al. [7] in this issue of the journal reports on the results of a randomized controlled trial with a very elegant design aimed to demonstrate the superiority of liver IA PRRT with [^{177}Lu]Lu-DOTATATE. They performed an IA injection of one liver lobe in patients with bilobar NET metastases, with the contralateral lobe serving as control ("in patient control"). The later will only be reached by radiopharmaceutical that has gone through the liver vascular bed and passed in the right atrium to the systemic circulation, mimicking an IV injection. The patients were randomized for right vs. left lobe injection and the liver perfusion territory was mapped using cone-beam CT, a tool that has been show to accurately delineate the tissue reached from a specific catheter position in IA liver-directed treatment [8]. The primary endpoint was the normalized tumor uptake (tumor-to-normal liver) on the post-therapy SPECT 24 h post-injection of the first PRRT cycle. It was determined for the IA-injected lobe and compared to the one of the non-IA injected lobe. This strategy allows to

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control for the highly variable patient characteristics in the patient population treated with PRRT, with variation in primary tumor, Ki-67 index, tumor burden, vascularization of lesions, SSTR expression, use of concomitant somatostatin analogues (SSA), etc. Furthermore, the measure of the endpoint is available the day after treatment and does not require follow-up such as objective imaging response or PFS and OS, which can require months to years due to the slow growth kinetics of many SSTR positive NETs and the substantial efficacy of [^{177}Lu]Lu-DOTATATE PRRT.

Their results might be disappointing at first glance and bring to mind Thomas Huxley's famous aphorism "The great tragedy of science: the slaying of a beautiful hypothesis by an ugly fact." Indeed, they did not observe a significant increase in T/N ratio in the IA injected liver lobe compared to the control lobe: 17.4 vs. 16.2 ($p = 0.299$). Not surprisingly, they did also not observe a difference in response rate at 3 and 6 months in the lesions in the IA-injected lobe vs. the non-IA injected lobe. The observed toxicity was similar to toxicity observed in IV PRRT [1].

How can we reconcile these findings from a carefully designed and executed prospective therapeutic trial [9] with the current evidence about IA PRRT [10]? First, some publications have compared two different groups of patients, one treated with IA PRRT, the other one with IV PRRT. Comparing standardized uptake values (SUV) in different patients populations can introduce bias, as these can be highly variable and dependent on metastasis characteristics (SSTR expression, perfusion, etc.), and without randomization, there might have been a selection bias favoring IA therapy in patients with high SUV values in the liver metastases on SSTR PET. However, other publications have clearly showed higher SUV values in the same patient injected with IA and IV [^{68}Ga]Ga-DOTATOC in a short timeframe. Kratochwil et al. [11] showed a 3.75 increase in SUV favoring IA injection in a cohort of 15 patients scanned by both strategies within 4 weeks. One important difference between [^{68}Ga]Ga-DOTATOC and [^{177}Lu]Lu-DOTATATE that could explain, at least partially, these observations is the injected peptide mass. Indeed, for diagnostic imaging the mass injected per patient is typically in the order of ~ 10 µg per patient (e.g., Kratochwil et al.: maximum 24 µg/patient), whereas for therapy 100 or even 200 µg per patient is used [12]. The vast majority of these molecules do not contain lutetium-177 atoms and hence are involved in competitive blocking of SSTR binding of [^{177}Lu]Lu-DOTATATE. Ebbers et al. used commercially manufactured [^{177}Lu]Lu-DOTATATE (Lutathera®), which contains 200 µg per vial of 7.4 GBq, with < 10% of peptides containing lutetium-177 [12]. This effect is further compounded by the fact that this high mass amount is injected toward a single lobe, increasing the amount of unlabeled peptide delivered per unit of metastasis volume. It is likely that this resulted in blocking of a large fraction of the SSTRs in the liver metastases, preventing the accumulation of a higher amount of radioactivity. This effect could be even reinforced by circulating non-radioactive SSAs that are often continued during PRRT (e.g., Netter-1 regimen [1]). No specific information on the use of non-radioactive SSAs is provided in Ebbers et al.; patients were allowed to stay on SSA at physician's discretion (Braat A., personal communication).

One other reason that Ebbers et al. advance as potential explanation for not reaching the primary endpoint is the relatively high vascularization of the liver, which by itself could be already sufficient to administer a high amount of radiopharmaceutical to the metastases. The cardiac output in a normal person is ~ 20% to the liver [13] and ~ 20% to the kidney [14]. This means that a substantial fraction of the radiopharmaceutical will never pass through metastatic lesions and will be lost for tumor targeting trough urinary excretion. Furthermore, the vascularization of the liver is mainly driven by portal vein perfusion (~ 80%), but it is well know from CT and CBCT imaging that NET metastases are primarily irrigated by branches of the hepatic artery, which can further reduce the actual fraction of the cardiac output that reaches the liver metastases. So there is a real potential for the IA approach to deliver higher amounts of radiopharmaceuticals to liver metastases, as also shown by Kratochwil et al. Another interesting observation in the IA field is the radiopharmaceutical washout from the liver metastases, with values higher after initial injection but with increasingly narrowing differences with IV injection over time, up to 72 h post injection [15, 16]. Up to now it is not known what mechanism causes this increased washout. Finally, intracellular translocation of the receptor-ligand complex as such does not contribute substantially to the lack of efficacy observed by Ebbers et al., as this is the result of target engagement by a vector molecule and hence uptake of the administered drug by the tumor.

Should this trial mean the end of IA PRRT? On the contrary, this trial provides a very elegant and robust methodological framework for further evaluation of IA PRRT. Using intra-patient control, with CBCT mapping of perfusion territories and post-therapy imaging end-points, small cohorts of several tens of patients can provide compelling evidence on the potential benefit of a specific IA RNT strategy. Questions that could be addressed include the effect of high specific activity IA PRRT or PRRT using SST antagonists, which are known to bind to a substantially higher number of receptor configuration states, potentially allowing to bind a higher fraction of the delivered peptide mass. IA injection could also be examined in the development of RNT aiming at other molecular targets. As liver metastases are an important negative prognostic factor in prostate cancer patients, injection of [^{177}Lu]Lu-PSMA in patients with PSMA positive liver metastases could be envisioned. A particular case would be

radiopharmaceuticals with short tumor retention time, where short-lived radionuclides can be an attractive option and hence a rapid tumor targeting is warranted (e.g., fibroblast activation protein inhibitors and bismuth-213). Finally, other sites could be envisioned, such as the brain with PRRT in meningioma or the splenic artery for lymphoma. Optimization of radionuclide therapy through intra-arterial injection should be continued to be studied and the methodological framework developed by Ebbers et al. constitutes a very good guide.

Declarations

Ethical approval Not applicable to this editorial.

Consent to participate Not applicable.

Conflict of interest The author declares the following conflicts of interest. CMD is/has been a consultant for Sirtex, Advanced Accelerator Applications, Novartis, Ipsen, Terumo, and PSI CRO. He has received travel fees from GE Healthcare, Sirtex.

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