Chapter 10

FUTURE PERSPECTIVES AND CONCLUSIONS

Radiolabelled somatostatin analogues have been used in the treatment of neuroendocrine tumours (NETs) for more than a decade. Several clinical trials have indicated that peptide-receptor radionuclide therapy (PRRT) with 90Y-DOTATOC and 177Lu-DOTATATE is an active therapeutic tool in the management of NETs. Present knowledge and clinical studies indicate that it is possible to deliver high activities, and therefore high absorbed doses, to tumours expressing sst2 receptors, with achievement of partial and complete objective therapeutic responses in up to 30% of patients. Side effects, involving the kidney and the bone marrow, are mild if adequate renal protection is applied [1-5]. Nonetheless, being PRRT a relatively young therapy, much is still to be understood and explored, and researchers are trying to give an answer to the present limitations and unresolved issues. PRRT, in fact, was born at the beginning of the nineties as the next logical step to hormonal peptide biotherapies in endocrine tumours, a new frontier in nuclear medicine therapy, and from the beginning prompted an enthusiastic use in clinical trials, although sometimes conclusions on the efficacy, particularly towards other therapies, were drawn from studies not oncologically designed for that purpose. To this respect, results, mainly with 90Y-DOTATOC, have been inferred from many phase I-II studies, carried out by various groups, but rather poor in patient number and inhomogeneous as to patient selection, inclusion criteria, and treatment schemes [4]. Therefore, an inter-study comparison is virtually impossible. Clinical phase II and III trials have been skipped, and today the use of PRRT has become quite customary, following eagerly the many brilliant results obtained in patients. Still many data lack, but an oncologically correct sequence of clinical trials seems now out of season. Actually, the accomplishment of such studies in nuclear medicine, and the consequent knowledge on large numbers of patients, appears rather difficult to obtain, for many reasons, logistical, economical and political. Nevertheless, today, already existing radiopeptides and PRRT techniques can be improved.

The exact anti-tumour efficacy of these molecules in single classes of diseases and in single clinical categories is still not fully defined. Theoretical considerations and animal studies demonstrated a better suitability of Lutetium-177 in smaller lesions and of Yttrium-90 in larger lesions, but, to date, 90Y-DOTATOC and 177Lu-DOTATATE have not been comparatively studied yet, in proper phase III studies. Moreover, almost all the studies carried out to date focussed merely on anti-tumour activity and, unfortunately, due the small numbers and relatively short follow up, still cannot demonstrate with formal oncological significance the impact of PRRT on the most important aim in oncology, namely the overall survival, or at least its surrogate end-point, time-to-progression (TTP). The recent data from the Rotterdam group on the survival of 310 patients treated with 177Lu-DOTATATE indicate clearly an important survival in patients undergoing PRRT, with 48 months median disease related survival and, particularly important, a 40 month TTP. A rough comparison with historical groups from the literature undergoing other therapies indicate a consistent survival benefit [6]. Therefore, the information
deriving from this study is that in several patients PRRT has a largely superior cost/benefit ratio towards chemotherapy, and allows avoiding unnecessary toxicity. Nevertheless, to date the exact quantification of this benefit must still be assessed once and for all by means of specifically designed phase III trials.

A further consideration can be made on the need to identify the patients who are going to respond to PRRT and their specific biological parameters, such as Ki-67 proliferation index, besides the known basal OctreoScan uptake and disease extension.

Apart from radiobiological speculations regarding the better irradiation of the smallest disease as possible, the exact place of PRRT in the therapeutic algorithm of NETs is still unknown.

In addition, the possible renal and bone marrow toxicity is still not fully understood and remains something that scares clinicians, particularly the referring oncologists. Radiation burden to tumour and normal organs, in fact, is difficult to establish with satisfactory accuracy. Nevertheless, treating patients with an excessively conservative approach, not considering the individual dosimetry, may limit in turn the efficacy of treatment.

Safety is the dark side of the moon in radionuclide therapy with radiopeptides and individual dosimetry of normal organs and tumour is a preliminary step for patient selection and therapy planning, necessary because there are huge differences amongst patients as to the radiopeptide uptake in normal organs and tumour tissues.

In PRRT with $^{90}$Y-peptides, dosimetry is reconstructed either from simulation with the $^{111}$In-labelled peptide, biochemically similar but not identical to the original one, and the simulation with the $^{86}$Y-labelled peptide, mimicking in every respect its therapeutic counterpart [7,8]. To date, no study comparing the two simulations in the same patients was carried out. In $^{177}$Lu-DOTATATE therapy, the gamma emissions of Lutetium-177 allow for dosimetry and imaging during the therapy. On a theoretical basis, the physical properties of Lutetium-177 make it a better candidate for the irradiation of smaller lesions. Unfortunately, to date a thorough dosimetric analysis is still lacking, but data deriving from a study comparing $^{177}$Lu-DOTATATE to $[^{111}\text{In-DTPA}^0]$-octreotide indicate lower burden to organs. Again, researcher must answer these open issues.

The major task for PRRT is to deliver the maximal detrimental dose to the tumour while limiting as much as possible the irradiation of normal organs. Currently, the potential risk of kidney and red marrow limits the amount of radioactivity that may be administered. Indeed, when tumour masses are irradiated with suitable doses, volume reduction may be observed [9]. Clinical experience and dosimetric studies clearly indicate that patient-specific organ volume and intra-organ distribution of the radionuclide, such as in the kidney, are crucial for a correct estimate [10] and should be taken into consideration in the organ dose calculation. New Monte Carlo analyses, accounting for the difference in radioactivity placement in organs such as the kidneys, by a CT-based volumetric analysis, appear more realistic. Moreover, being PRRT a form of continuous radiation delivery with a decreasing dose-rate with time, causing both lethal and sublethal damage, the newly proposed BED model appears to be a reliable predictor of toxicity and could thus be helpful in implementation of individual treatment planning [10]. In this view, a correlation of the dosimetric parameters with the radiobiologic features could offer a better
comprehension of the actual phenomena and could allow a patient specific tailored treatment, as to the of the tumour irradiation and the tolerability of normal organs. Therefore, researchers must fill this gap to define the characteristics and the role of PRRT in the management of NETs, and, most important, to reach the necessary authorizations from regulatory organizations for the commercialization and broad diffusion of these radiopharmaceuticals.

Today the issues of developing new molecules and techniques can be depicted as how to increase the therapeutic index, thus increasing the efficacy, while lowering the possible toxicity. In the past ten years, together with the development of PRRT, also the knowledge and studies on the physiopathology of somatostatin and other G-protein coupled receptors increased, thus offering new strategies to be exploited in therapy.

In order to increase the anti-tumour efficacy, improvements must lead to an increased tumour uptake, thus involving new radiopeptides with high receptor affinity and wide distribution on tumours, modification of the targeted receptors, and combination therapies.

NETs and human cancer in general, may overexpress receptors, usually G-protein coupled receptors, for a variety of peptides simultaneously, such as somatostatin, bombesin, vasoactive intestinal peptide, cholecystokinin, substance P, GLP-1, neurotensin \[11,12\]. The ligand–receptor system that has been most extensively exploited in clinical nuclear medicine practice is based on somatostatin, which can be considered as the prototype. Classically, the receptor-mediated internalization and intracellular retention into the endosomes of a radiolabeled peptide has been considered as the biologic basis for receptor radionuclide therapy \[13\]. Nevertheless, new studies, testing the direct and selective irradiation of a cell target from the sole receptor binding of non-internalizing radiopeptides such as receptor antagonists, are changing this dogma. Recent studies demonstrated that radiolabelled antagonists for the sst$_2$ and sst$_3$ have more binding sites than agonists with comparable receptor affinity. This proved to compensate for the faster receptor dissociation, yielding higher tumour uptake and lower tumour-kidney ratios in the animal. \[14\].

Moreover, recent observations have shown that internalization of human somatostatin receptor subtypes could be determined by functional homo- and heterodimerization between somatostatin receptors or other G-protein-coupled receptors, such as dopamine D$_2$ receptor, with resulting properties that differ completely from those of the individual receptors as to ligand-binding affinity, signalling, agonist-induced regulation, and internalization \[15,16\]. In view of the dimerization phenomenon, new agonists either superselective, chimeric, or panagonists could represent a new option in peptide receptor radionuclide diagnosis and therapy.

Other radiolabelled G-protein coupled receptor ligands have been developed in pre-clinical and clinical setting. These include bombesin analogues, agonists or antagonists, the latter again possibly superior for the higher uptake, targeting GRP-receptor rich tumours, such as prostate or NETs \[17\]; pan-cholecystokinin (CCK) receptor binding ligands, such as minigastrin, targeting medullary thyroid, small-cell lung or colorectal carcinomas, that have been tested in human \[18,19\]; Substance-P analogues, such as exendin-4, targeting GLP-1 receptors in insulinomas \[20\].
Somatostatin analogues represent to date the prototype and the most successful paradigm of radiopeptide therapy, due to the fortunate discovery of a successful class of synthetic peptides, such as octreotide and its variants, and to the inhibiting properties of somatostatin and its analogues, which induce few and limited side effects. Present limitations to the human use of other receptor peptides are the relative poor stability in plasma of the molecules currently available for human use, the strong kidney uptake deriving from their high hydrophilicity, and the occurrence of pharmacologic stimulation effects with many of the agonists, such as those of bombesin or CCK receptors [21-23].

In order to increase the uptake of the radiopeptide, actions can be directed also towards the targets, by inducing an increase in receptor number. This could be obtained by means of gene therapy, by delivering the gene of somatostatin or other receptors inside the tumour cell via a viral vector [24,25], or by stimulating receptor up-regulation, in turn obtainable with a low-dose first therapy [26]. However, to date, these actions remain difficult to translate to patients.

Nowadays, combination therapies seem a more practicable and fruitful pathway, in order to obtain synergistic and sensitizing effect to PRRT. Following new tendencies in oncology, namely the combination of cytotoxic with bioactive drugs, main tendencies in nuclear medicine therapy are directed towards the combined use of PRRT with antiangiogenic drugs, e.g. anti-VEGF, such as bevacizumab, or PRRT with anti-EGFR biodrugs, such as cetuximab [27]. Combination therapies include also the use of PRRT and radiosensitizer chemotherapy, such as capecitabine. A new randomized, controlled clinical multicenter trial comparing the safety and efficacy of the combination of \(^{177}\)Lu-DOTATATE and low dose capecitabine versus \(^{177}\)Lu-DOTATATE as single agent, is presently ongoing, after a feasibility study indicating the antitumour potential and the limited side effects of the combination [28].

Combination therapies represent seemingly the most concrete way for treating most forms of cancer in general, and NETs specifically, also considering their relative indolence. In the light of these new tendencies in oncology, it must be remembered that PRRT with radiolabelled somatostatin analogues has not its most appropriate indication in extremely advanced clinical situations (a sort of “rescue therapy” for terminal patients), but must be considered, to any respect, as a frontline anti-tumour treatment, to be performed preferably early in the treatment schedule of neuroendocrine or other cancers, and to be investigated and evaluated as any other oncologic tool.

The newly proposed and mostly discussed radiopeptide candidates for future PRRT are the result of a change in the theory of peptide receptor therapy, namely the chimeric somatostatin analogues binding dimerized cross-talking receptors, and the bombesin or somatostatin receptor non-internalizing antagonists. The possible application of these peptides in clinical trials will be guided from the current experience on safety and efficacy of PRRT and from the exploration of the present open issues.

References


