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Clinical Applications

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Successful radionuclide therapy today: Therapy with I-131 (sodium iodide) is the most widespread application of radionuclide therapy. It is effective in the management of thyroid cancer and benign thyroid disease. Due to the excellent selectivity of iodine for thyroid tissue, high radiation doses can be delivered to the target tissue, while sparing other tissues and organs. Side effects are usually mild, and the risk of secondary cancers is low. Therapy with I-131-MIBG can be successfully applied in patients with pheochromocytoma, neuroendocrine tumours and neuroblastoma. Bone marrow is the critical organ, but severe long-term marrow toxicity is rare with standard activities. The thyroid must be protected, since some I-131 will come free. Strontium-89 and bisphosphonates labelled with Re-186, Re-188 or Sm-153 are analogues of calcium or phoshate respectively, and can thus be used for palliation of painful bone metastases. These radiotherapeutics bind to highly metabolic bone and not to the tumour itself, but even anti-tumour effects and survival benefits have been reported. The main excretion route is via the kidneys, but due to lack of renal retention, the renal radiation burden is relatively low and bone marrow is the critical organ. Local therapy (e.g. Y-90 labelled particles in joints or cavities) can be very successful because all the radioactivity remains close to the target. Monoclonal antibodies are large proteins with a small portion of the molecule that binds specifically to a receptor. Penetration in solid tumours is problematic, but the long retention in the blood is favourable for targeting hematological malignancies. Anti-CD20 monoclonal antibodies, e.g. Y-90-Ibritumomab tiuxetan (Zevalin) or I-131-Tositumomab (Bexxar) are successfully used in the treatment of non-hodgkin lymphoma with high remission rates and improved survival. Again, bone marrow is the critical organ.

Radiolabelled peptides are small molecules with fast blood clearance and high binding affinity to receptors. Peptide receptor radionuclide therapy (PRRT) with the third generation of therapeutic somatostatin analogue, Lu-177-DOTA-octreotate is effective in patients with advanced neuroendocrine tumours. Most of these tumours express somatostatin type 2 receptors to which Lu-177-DOTA-octreotate has very high affinity. Many patients have reduction or stabilisation of tumour size, less symptoms and better survival. Critical organs are bone marrow and the kidneys, because of some retention of the radiopeptide in the kidneys. Protective measures to diminish the renal retention, and thus the radiation dose to the kidneys are essential. Alternative peptides for radionuclide therapy have been less successful so far, due to lower receptor affinity, less favourable biodistribution (e.g. very high renal uptake), fast degradation after injection, etc.

Concepts and strategies for success: The above outlined current radiopharmaceuticals for therapy have several common properties. A therapeutic radiation dose is delivered at the target, while avoiding too much toxic radiation to critical organs and the rest of the body. To achieve a high target to background ratio, it is essential that the affinity for the target is (very) high, and that the retention of the intact compound (or the radioactive metabolite) is long. Radioactive compounds that are stable in vitro or in animal models may prove to be unstable in the human setting. New strategies for improvement of binding may include upregulation of receptors, using antagonists instead of agonists, transfection to induce receptors, to use molecules that bind to more than one type of receptor or to use cocktails of radioligands aimed at different receptors. In such strategies, increased nonspecific background activity should be avoided. The choice of radionuclide is important: high-energetic radiation (e.g. Y-90) may be necessary for adequate penetration in the tumour, but lower energies (e.g. from I-131 or Lu-177) may be necessary to avoid toxicity. Adequate dosimetry for tumors and normal organs and tissues is necessary to find the safe maximal limit for an individual patient. However, current dosimetric methods have limited predictive power for efficacy and toxicity in individuals (especially bone marrow dosimetry) and are not always practically feasible for routine clinical use. Once at the target, the effects of the radiation may be enhanced by combination with chemotherapy (radiosensitizers), or compounded effects of therapy (e.g. surgical debulking and targeted radiation) may be more effective than either modality alone.

Strategies for lowering radiation effects to the critical organs (reduction of renal uptake; radical scavengers (e.g. amifostine) to protect normal tissue, long-term renal protection (e.g. angiotensin II-inhibitors) or even bone marrow transplant) can help to widen the therapeutic window. Finally, clear definition of treatment goals (cure, "quality of life", survival), close collaboration with clinicians and clear experimental protocols (phase 1, 2, 3 trials) may facilitate registration for general use (EMEA, FDA) and widespread acceptation.