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New therapeutic radioisotopes

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Looking at the chart of radionuclides we can find about 1 % of them suitable for therapy. Although these are long known they may be newly included in the list of therapeutic isotopes. How do we select suitable therapeutic nuclides?

The goal of radionuclide therapy is the killing of tumour cells through systemic accumulation of activity. Since the tumour properties are extremely variable, the pharmacological vectors (vehicles) have to be selected accordingly, which in turn leads to the selection of a radionuclide with properties matching the properties of the vehicle.

The most important factors are the half lives, namely the physical half life of the nuclide and the biological half life of the radiopharmaceutical (RPH). The latter is basically defined by the vehicle, but the chemical properties of the radionuclide, the chelator which binds the nuclide and the tether between chelator and vehicle also influence the behaviour of the RPH. In general, the maximum of the tumour uptake of an antibody is seen within a few days and that of a peptide within a few hours after injection. If we would use a short-living radionuclide together with an antibody, most of the disintegrations would take place before the activity reached the tumour, while a long-living radionuclide together with a peptide would show most of the disintegrations after excretion of the activity.

A second important factor is the property of the emitted radiation, namely, α, _¯, γ and auger electrons. In the contribution of S.E.Strand, "New dosimetric methods", the influence of the property of the emitted radiation on the tumour dose will be discussed in detail. Briefly, we need different kind of nuclides with emission of _¯ particles with high or low energy, α particles, and auger electrons, depending on the size of the tumour or the localisation of the vehicle. The γ radiation, although contributing to an unwanted whole body dose, is quite useful for the detection and follow up of the in vivo distribution of the RPH.

The third factor is the chemical property and the production route. If the vehicle is used to target a receptor, usually a very high specific activity is needed. Thus, the radionuclide should be produced in a "no carrier added" (nca) manner or at least with a minimal amount of accompanying inactive isotopes. The irradiation with protons or neutrons followed by the separation process should yield a high amount and a high purity of the radionuclide.

The group of rare earth metals comprises a few interesting radionuclides which can be bound with the DOTA (or DO3A) chelator to any vehicle (1). The nuclides (half life, Emax, carrier) are ^{153}Sm (46.75 h, 0.8 MeV, ^{152}Sm), ^{149}Pm (53.1h, 1.1 MeV, nca), ^{166}Ho (26.8 h, 1.9 MeV, ^{165}Ho), and ^{177}Lu (6.71 d, 0.5 MeV, $^{175/176}$Lu). A nca-route exists for ^{177}Lu with ^{176}Yb as educt but is much more expensive than the neutron activation of natural (or enriched) lutetium because of the about 1000 fold lower yield and the need of a separation procedure.

With respect to energy and half life but not chemical properties ^{67}Cu (61.9 h, 0.6 MeV) can be compared with the rare earth elements (2). It is obtained with proton bombardment of zinc and contains traces of inactive copper which is omnipresent. The tetra-aza macrocycles are ideal chelators to label the vehicles because they form complexes with Cu^{2+} of unique stability.

Rhenium and technetium (186Re, 188Re and 99mTc) are an example of a matched pair of radionuclides for both diagnosis and therapy (3). ^{186}Re (90.6 h, 1.1 MeV) is available either with carrier (^{185}Re) if it is obtained by neutron activation or as a cyclotron product (nca) with the drawback of possibly insufficient radionuclide purity (presence of ^{184}Re). ^{188}Re (17 h, 2.1 MeV) is available (like ^{99m}Tc) as a generator nuclide, namely the daughter of ^{188}W. The mother nuclide is produced by a double neutron capture, with a sufficient yield with access to a high flux neutron source.

Alpha-particle therapy (4, 5) is interesting because of the high energy deposit per disintegration and the very high LET (linear energy transfer). The most convenient radionuclide representing this group is ^{211}At, which can be produced by the ^{207}Bi(α,2n)^{211}At reaction. The half life of 7.2 h suggests that the use in combination with small molecules is more promising than with antibodies. Since At is a congener

of iodide, the chemistry is similar, however good yields and stabilities are not easily achieved. Other examples are ^{212}Bi (and the in vivo ^{212}2Pb-^{212}Bi in vivo generator) or ^{223}Ra. The latter can be used to treat bone tumours since it is a congener of Ca and Sr, and thus, accumulates in the bones in the chemically easily accessible form of the $^{223}Ra^{2+}$ cation.

References

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