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Pre-Clinical Studies in Animal Models

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Three phases can be envisaged in a pre-clinical study of a novel radiotherapeutic agent: (i) Selection of an appropriate animal model; (ii) acquisition of biodistribution or efficacy data (iii) interpretation of the data and extrapolation to human application.

Selection of animal models. For most pre-clinical studies small rodents such as mice and rats are used. Although mice are cheaper and provide a greater range of potential models the small size of the organs present problems in data interpretation. Radiopharmaceuticals are distributed in vivo by what might be termed 'specific' and 'non-specific' mechanisms. Specific uptake occurs through interaction of the tracer with the molecular target of choice and this target while non-specific uptake occurs as a result of perfusion, excretion, metabolism or immune recognition and occurs in normal tissues. Both types of uptake can occur in both diseased and normal tissues but specific uptake tends to dominate in the former and non-specific uptake in the latter. The ideal animal model will allow both uptake mechanisms to be assessed. Many molecular targets of interest such as neuropeptide receptors are expressed on normal tissues. Normal animals can therefore sometimes be used to assess the interaction of targeting agents with these receptors provided that differences in the levels of receptor expression in normal and diseased tissues and species differences between mouse and man are borne in mind. Since the rationale for most tumour targeting is enhanced expression of target receptors then tumour-bearing models are, in most instances, the animal model of choice. Receptor-positive tumour cells derived from humans or rodents can readily be transplanted into immunodeficient mice or rats and the use of transfected cell lines provides a means of precise selection of molecular target. Points to consider in selection of the cell line include levels of target expression, species of origin and, especially with regard to transfected lines, receptor functionality after ligand interaction. Transgenic animals provide a valuable mechanism for engineering in-vivo expression of molecular targets that are not normally expressed in rodents – antibody epitopes for example. Importantly, such models can provide expression on both diseased and normal tissues.

Acquisition of data. Two types of studies are commonly performed; Biodistribution data can be generated on which dosimetry calculations are performed to predict the likely radiotherapeutic effects. This biodistribution data can be obtained using either PET or SPECT imaging or kill, cut and count approaches. Imaging has the advantages that fewer animals are required since serial imaging studies can be performed on the same animals at a large number of time points if desired. However, they have the disadvantage that absolute quantification of uptake, especially in smaller or diffuse organs is difficult. Dissection and counting of tissues from animals provides a simpler and more accurate assessment of radioactive tissue distribution and much greater resolution is possible, but requires much greater numbers of animals especially if data is required for many time points. This has both ethical and cost implications. The second type of study to be performed are efficacy studies in which the radiotherapeutic effect of the agent is determined directly, normally in tumour-bearing animals.

Interpretation of data. Great caution should be exercised in extrapolating both biodistribution and efficacy data obtained in animal models to the human situation. Specific uptake differs between mouse and man due to differences in molecular target expression profiles. Non-specific uptake differs owing to differences in normal organ perfusion and factors influencing the rate and route of excretion. The biological effect of targeted radiation will also differ because of differences in rates of cell turnover but most importantly because of the size of the animal in relation to the path length of the radionuclide employed. For a high energy beta-emitter such as Y-90 for example the individual tissues will be irradiated from radioisotope deposited almost anywhere in the body. In general, the best approach is to perform draw conclusions from comparisons of a novel agent with a 'gold standard' examined in the same model.

References

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