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Alpha therapies present practice and future prospects

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The role of beta emitters has become firmly established in the treatment of both benign and malignant disease over the past 60 years. However the degree of penetration of betas can lead to significant co-morbidity for example with Y-90 octreotate it has been shown to result in both renal and bone marrow toxicity (1). Therefore over the past 5 years there has been the increasing re-interest in the use of alpha therapies. Alpha particles are helium nuclei and as they have both charge and mass are able to inflict significant damage on tissues. In high concentration they have been used for political assassination (2). Their penetration in tumour is limited to about 1-10 nm, possibly no more than 10 cells often less. During that track they deposit GeV worth of ionizing radiation 1000x that of a typical beta emitter.

Therefore the concern with alpha emitters is that there must be very good targeting to ensure efficacy without toxicity.

On the other hand shielding is easy as no alphas will penetrate the plastic chamber of the average syringe. A further complication is that most alpha emitters are heavy metal with complex chemistry made more complex by decay chains which make most chemists weep. For example Ac-225 decays to Fr-221 which decays to Ac 217 which decays to Bi213. Bi2013 may undergo alpha decay to Tl-209 or beta decay to Po213. the advantage is that with alpha emitters you get multiple decays some a few seconds or minutes apart good for tumour kill but the chemical nature of the daughters change so much it is a chemists nightmare. How do you design a ligand that allows actinium than francium than back to actinium; meanwhile keeping everything on target.

This has resulted in some novel ideas about delivery of these agents this would include topical applications for skin lesions and intra-tumoural injections of the alpha emitters.

Examples include uses of B-213 labelled antibodies injected directly into melanoma plaques. This has been done in both animal models and man (3)

A similar approach is the use of ant-tenascin antibodies labelled with As-211 injected into the CNS or tumour cavity via an Omaya reservoir (4) with some encouraging early results in man.

However the first alpha emitter that will become commercially available uses a simpler and more direct route. Radium is a calcium analogue which replaces calcium in the bone matrix and in its form as Rd232 is an alpha emitter.

This product has finished phase 2 trials in metastatic prostate cancer and is now included in an international phase 3 trial. The protocols are slightly different than with Sr-89 and Sm-153 EDTMP as the aim was to reduce tumor mass so patients were injected with about 10MBq Rd 232 4 weekly for 4 months and this compared to placebo. Whilst those with placebo had disease progression, those patients receiving Rd-232 showed disease regression of their bone metastases (5).

So the exciting era of alpha therapies is around the corner we should be prepared to add these agents to our armory

References:

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Experience comparing Bi-213 with Lu-177 in a prostate cancer model

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Abstract not available