Radioimmunotherapy of small solid tumours using monoclonal antibodies labelled with Auger electrons emitters

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Introduction: The efficiency of 125I in killing tumour cells was compared in vitro and in vivo according to whether the emitter was localised at cell surface or within cytoplasm. Materials and methods: In in vitro experiments, the A-431 and SK-OV-3 carcinoma cell lines expressing the HER1/CEA and HER2/CEA receptors, respectively, were incubated for 2 days with either internalising (anti-HER1 or anti-HER2, respectively) or non-internalising (anti-CEA) 125I-labelled monoclonal antibodies (mAbs). Uptake of radioactivity per cell was measured and used for determining the mean nucleus irradiation dose according to the MIRD cellular approach. Relationship between clonogenic survival and the mean nucleus irradiation dose was next investigated using a linear mixed regression model. In vivo efficiency of 125I-labelled mAbs was also assessed in radioimmunotherapy of small solid tumours. Swiss nude mice bearing intraperitoneal A-431-xenografted tumours (<2mm) were then intravenously injected with 2 x 1mCi of either internalising or non-internalising 125I-mAbs. Tumour growth was followed by the bioluminescence technique. Uptake of radioactivity per organ was determined through a biodistribution assay and Monte carlo-calculated S-factors previously published for voxel-based mouse model were then used for dose assesment. Results: In vitro, we showed that toxicity of non-internalising mAbs was either greater or similar to the one observed with internalising mAbs suggesting the involvement of the cell membrane in radiation response to Auger electrons. In vivo, we confirmed the efficiency of 125I-labelled mAbs in the therapy of small solid tumours. Median survival time (MST) was about 19 days in non-treated mice. It was not statistically increased when the unlabelled non-internalising mAb was used (MST= 24 days). By contrast, unlabelled internalising mAb was shown to significantly increase survival (MST=76 days, $p<0.001$). Labelling non-internalising mAb with 125I was accompanied by a significant increase in survival (MST = 67 days, $p=0.004$) while it had no effect on efficiency of internalising mAb (MST= 77 days, $p=0.80$). Irradiation doses delivered to organs and tumors were also assessed. Conclusion: This study demonstrates in vitro and in vivo the efficiency of non-internalising 125I-mAbs in radioimmunotherapy of small solid tumours. It indicates that the cell membrane is a sensitive target to Auger electrons.

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