Alpha-radioimmunotherapy with Astatine-211

Evaluation and imaging of normal tissues and tumors

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Abstract

Alpha-radioimmunotherapy (α-RIT) is an internal conformal radiotherapy of cancer using α-particle emitting radionuclides. Alpha-particles have a very short range in tissues (<100 μm) and high linear energy transfer (LET), making them highly cytotoxic. Due to these characters α-emitters are potentially highly effective in eradication of small tumor cell clusters while at the same time toxicity of the adjacent normal tissue is avoided. Thus, α-RIT could be effective in treatment of cancers characterized by micrometastatic and minimal residual disease, e.g. ovarian and prostate cancer.

The biological effects of α-particles are grossly unknown and demand dedicated methodologies and evaluations for their interpretation. The aim was to evaluate the irradiation effects of the α-particle emitter ^{211}At for its use in α-RIT, using nude mice. This included studies on tumor efficacy, kidney toxicity and a study describing a novel bioimaging system, the α-camera, for assessment of radionuclide tissue distribution.

Growth inhibition (GI) after α-RIT with ^{211}At on s.c. OVCAR-3-tumors was compared with GI after external irradiation using ^{60}Co. For α-RIT, the mice were injected with ^{211}At-MX35-F(Ab')$_2$ at different activities. The GI was calculated for both irradiations and used to estimate the relative biological effectiveness (RBE) for α-RIT on tumors. At GI of 0.37, the RBE was found to be 4.8±0.7.

The long-term renal function after α-RIT was studied by measuring the glomerular filtration rate (GFR) after injection of ^{211}At-MX35-F(Ab')$_2$ at different activities. The GFR was measured repeatedly, using plasma clearance of ^{51}Cr-EDTA, up to 67 weeks after treatment. Dose-dependent and time-progressive reductions in GFR were found. For tumor-bearing mice, the kidney doses required for 50% reduction in GFR were 16±3.3 and 7.5±2.4 Gy at 8-30 and 31-67 weeks, respectively. For non-tumor-bearing mice the corresponding doses were 14±4.1 and 11.3±2.3 Gy. The maximum tolerable dose (MTD) to the kidneys (50% reduction in GFR) was 10 Gy.

A novel imaging system for ex vivo detection and quantification of α–emitters in tissues was developed, using an autoradiographic technique based on a scintillator and CCD for light detection. Initial evaluations of the imaging characteristics showed that the spatial resolution was 35 ±11 μm, the uniformity better than 2% and that the image pixel intensity was proportional to radioactivity in the imaged specimens. As examples of applications, the α-camera visualized and quantified differences in the tissue activity distributions after α-RIT with ^{211}At. For tumors, a very nonuniform distribution of ^{211}At-MX35-F(Ab')$_2$ was found from 10 mpi to 6 hpi. At 21 hpi the distribution was more uniform. Images of kidney-sections could identify the ^{211}At-distribution in different renal compartments. The 'cortex-to-whole-kidney-ratio' varied with time and bioconjugate size. The ^{211}At-MX35-F(Ab')$_2$ showed a marked retention in the renal cortex, corresponding to a ratio of 1.38±0.3 at 2 hpi.

The RBE found (4.8±0.7) gives further support for the use of α-particles in targeted radiotherapy. The MTD of 10 Gy suggests that the kidneys will not be the primary dose-limiting organ in α-RIT with ^{211}At. The α-camera will be an important tool for internal α-particle-dosimetry and for the development of α-RIT.

Keywords: astatine, alpha-particle, RBE, radioimmunotherapy, renal function, GFR, imaging, targeted alpha therapy

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I.
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II.
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