

ALPHA-PARTICLE EMITTER THERAPY: OVERVIEW, CURRENT STATUS, AND DOSIMETRY

G. Sgouros

Div. of Nuc Med, Dept of Radiology, CRB II 4M.61, 1550 Orleans St. Johns Hopkins University,
School of Medicine Baltimore, USA
Email: gsgouros@jhmi.edu

The potential of alpha-particle emitters to treat cancer has been recognized since the early 1900s. Targeted delivery of alpha-emitters provides the fundamental advantage of a more potent, cytotoxic type of radiation. Alpha-particles are helium nuclei that deposit DNA damaging energy along their track that is 100 to 1000 times greater than that of beta particles; the damage caused by alpha particles is predominately double-stranded DNA breaks severe enough so as to be almost completely irreparable. This means that a small number of tracks through a cell nucleus can sterilize a cell and that, because the damage is largely irreparable, alpha-particle radiation is not susceptible to resistance as seen with external radiotherapy (e.g., in hypoxic tissue) and chemotherapy (e.g., due to quiescence). Animal and cell culture studies have shown that, per unit absorbed dose, the acute biological effects of alpha-particles are 3 to 7 times greater than the damage caused by external beam or beta-particle radiation. Although one might expect that this high potency against targeted cells would also be accompanied by high toxicity to normal bystander cells, the short, 50 to 100 micron range of alpha-particles limits the amount of damage that is incurred by normal tissue. Advances in the targeted delivery of radionuclides, in radionuclide conjugation chemistry, and in the increased availability of alpha-emitters appropriate for clinical use have recently led to patient trials of alpha-particle-emitter labeled radiopharmaceuticals. Although alpha-emitters have been studied for many decades, their current use in humans for targeted therapy is an important milestone. The following alpha-particle emitters are currently in use or being investigated for use in human trials: astatine-211 (^{211}At , 7.2 h), bismuth-212 (^{212}Bi , 1 h), bismuth-213 (^{213}Bi , 45.6 min), radium-223 (^{223}Ra , 11.4 d), actinium-225 (^{225}Ac , 10.0 d) and thorium-227 (^{227}Th , 18.7 d). The short-lived alpha-emitters, ^{211}At and ^{213}Bi have both been investigated as radioimmunotherapeutics in human clinical trials. Astatine-211, has been used to treat glioblastoma and ovarian carcinoma patients; ^{213}Bi has been investigated in leukemia patients. Peptide-conjugated ^{213}Bi has also been investigated in glioblastoma patients. The longer-lived alpha emitters, ^{223}Ra and ^{225}Ac have also been used in human trials. Radium-223 has been used as a radium chloride ($^{223}\text{RaCl}_2$) to target skeletal metastases in hormone refractory prostate cancer patients. Actinium-225 has been used as an immunoconjugate against leukemia. These alpha-emitters have shown substantial and highly significant efficacy with minimal toxicity in clinical conditions that are otherwise untreatable. In addition to these clinical studies, there are extensive pre-clinical efforts in lymphoma, melanoma, pancreatic, gastric and breast carcinoma and also in bladder cancer using ^{213}Bi . The generator system $^{211}\text{Pb}/^{211}\text{Bi}$ has been investigated, in combination with chemotherapy against a disseminated peritoneal disease model. Astatine-211 has perhaps the greatest history of pre-clinical investigation, encompassing numerous radiopharmaceuticals and pre-clinical models. Actinium-225, both as an immunoconjugate and as a radiopeptide has also

been investigated pre-clinically. A²²⁷Th immunoconjugate has been investigated against lymphoma. This combination of clinical studies and pre-clinical studies suggests that alpha-emitter therapy will continue to move to the clinic over the foreseeable future, the emphasis, to date has focused on targeting metastatic spread, including regional spread as in the glioblastoma and ovarian carcinoma cases. Current cancer treatment is rarely effective once the tumor has metastasized. The eradication of such metastases requires a targeted therapy that is minimally susceptible to chemo- or radio-resistance, that is potent enough to sterilize individual tumor cells and cell clusters and that exhibits an acceptable toxicity. Targeted alpha-emitter therapy holds great promise in meeting these requirements. Current constraints on this promise include the lack of widespread availability of alpha-emitters, the physics, radiochemistry and radiobiological-expertise required for their clinical implementation and also concerns regarding the potential toxicity of these agents.