Solid-tumor radionuclide therapy dosimetry: New paradigms in view of tumor microenvironment and angiogenesis

Xuping Zhu[a] and Matthew R. Palmer
Department of Radiology, Beth Israel Deaconess Medical Center, Boston, Massachusetts 02215

G. Mike Makrigiorgos
Radiation Oncology, Dana Farber-Brigham and Women's Cancer Center, Boston, Massachusetts 02115

Amin I. Kassis[b]
Department of Radiology, Harvard Medical School, Boston, Massachusetts 02115

(Received 4 January 2010; revised 28 April 2010; accepted for publication 29 April 2010; published 1 June 2010)

Purpose: The objective of this study is to evaluate requirements for radionuclide-based solid tumor therapy by assessing the radial dose distribution of beta-particle-emitting and alpha-particle-emitting molecules localized either solely within endothelial cells of tumor vasculature or diffusing from the vasculature throughout the adjacent viable tumor cells.

Methods: Tumor blood vessels were modeled as a group of microcylindrical layers comprising endothelial cells (one-cell thick, 10 μm diameter), viable tumor cells (25-cell thick, 250 μm radius), and necrotic tumor region (>250 μm from any blood vessel). Sources of radioactivity were assumed to distribute uniformly in either endothelial cells or in concentric cylindrical 10 μm shells within the viable tumor-cell region. The EGSnrc Monte Carlo simulation code system was used for beta particle dosimetry and a dose-point kernel method for alpha particle dosimetry. The radioactive decays required to deposit cytocidal doses ($\geq$100 Gy) in the vascular endothelial cells (endothelial cell mean dose) or, alternatively, at the tumor edge [tumor-edge mean dose (TEMD)] of adjacent viable tumor cells were then determined for six beta (^{32}P, ^{33}P, ^{67}Cu, ^{90}Y, ^{131}I, and ^{188}Re) and two alpha (^{211}At and ^{213}Bi) particle emitters.

Results: Contrary to previous modeling in targeted radionuclide therapy dosimetry of solid tumors, the present work restricts the region of tumor viability to 250 μm around tumor blood vessels for consistency with biological observations. For delivering $\geq$100 Gy at the viable tumor edge (TEMD) rather than throughout a solid tumor, energetic beta emitters ^{90}Y, ^{32}P, and ^{188}Re can be effective even when the radionuclide is confined to the blood vessel (i.e., no diffusion into the tumor). Furthermore, the increase in tumor-edge dose consequent to beta emitter diffusion is dependent on the energy of the emitted beta particles, being much greater for lower-energy emitters ^{131}I, ^{67}Cu, and ^{33}P relative to higher-energy emitters ^{90}Y, ^{32}P, and ^{188}Re. Compared to alpha particle emitters, a $\sim$150–400 times higher number of beta-particle-emitting radioactive atoms is required to deposit the same dose in tumor neovasculature. However, for the alpha particle emitters ^{211}At and ^{213}Bi to be effective in irradiating viable tumor-cell regions in addition to the vasculature, the carrier molecules must diffuse substantially from the vasculature into the viable tumor.

Conclusion: The presented data enable comparison of radionuclides used for antiangiogenic therapy on the basis of their radioactive decay properties, tumor neovasculature geometry, and tumor-cell viability. For alpha particle emitters or low-energy beta particle emitters, the targeting carrier molecule should be chosen to permit the radiopharmaceutical to diffuse from the endothelial wall of the blood vessel, while for long-range energetic beta particle emitters that target neovasculature, a radiopharmaceutical that binds to newly formed endothelial cells and does not diffuse is preferable. The work is a first approximation to modeling of tumor neovasculature that ignores factors such as pharmacokinetics and targeting capability of carrier molecules. The calculations quantify the interplay between irradiation of neovasculature, the surrounding viable tumor cells, and the physical properties of commonly used radionuclides and can be used to assist estimation of radioactivity to be administered for neovasculature-targeted tumor therapy. [DOI: 10.1118/1.3431999]

Key words: dosimetry, electron emitter, alpha particle emitter, tumor vascularity, neovasculature targeting, tumor targeting, targeted radionuclide therapy