INVITED COMMENTARY

Cancer Therapy with Auger Electrons: Are We Almost There?

The biologic toxicity of internally deposited radionuclides can be attributed to radiation-induced ionizations and excitations, nuclear recoil, chemical transmutations, and local charge effects. γ-Photons, x-ray photons, and energetic negatrons and positrons have a range of activity equivalent to many cell diameters and are characterized by low linear energy transfer and oxygen-dependent biologic effects. Radionuclides that decay by electron capture and/or internal conversion demonstrate an Auger effect; in this effect, extremely low-energy electrons (Auger, Coster-Kronig, and super-Coster-Kronig transitions) with subcellular ranges (nanometers) are produced. Monte Carlo calculations have been performed (*1–5*) to determine the electron spectra of commonly used Auger electron emitters, such as ^{99m}Tc (half-life [$t_{1/2}$], 6.05 h), ^{111}In ($t_{1/2}$, 2.1 d), ^{123}I ($t_{1/2}$, 13.3 h), and ^{125}I ($t_{1/2}$, 60.5 d). For example, the average Auger and Coster-Kronig electron spectra of ^{111}In, ^{123}I, and ^{125}I have totals of ~8, ~11, and ~20 electrons, respectively, with energies of approximately 12 eV to 24 keV (*1–3*). The ejection of the electrons leaves the decaying atoms transiently in a state of high positive charge. The burst of low-energy electrons results in highly localized energy deposition (10^6-10^9 cGy) in an extremely small volume (several cubic nanometers) around the decay site, and molecules in the immediate vicinity of the decaying atoms will be irradiated by these electrons. In addition, the dissipation of the potential energy associated with the high positive charge and its neutralization may act concomitantly and lead to some of the observed biologic effects.

Neglected initially for therapeutic purposes because of their low energy and consequent short range, Auger electron cascades are now being seriously considered. This shift in interest is, in part, a consequence of recent experimental findings that have altered some of the basic assumptions that previously limited the perceived therapeutic potential of Auger electron-emitting radionuclides.

Monte Carlo calculations, in which the low-energy, electron-emitting radionuclides (e.g., ^{125}I) had been positioned within or at very short distances (nanometers) from cylindric, "naked," double-stranded DNA, had predicted that 1 double-strand break would be produced per decaying atom (*6,7*). Although these theoretic expectations were later substantiated in studies with short strands of synthetic oligonucleotides, plasmids, phages, and bacterial DNA (*8–13*), recent studies have demonstrated that the decay of ^{125}I in mammalian cell DNA (i.e., supercompacted heterochromatin) leads to the production of $\gg$1 double-strand break per decay (*14,15*).

For years, the deleterious effects of low-energy electron emitters in mammalian cells had been attributed solely to direct ionization of DNA, the quintessential genetic target. Here again, it has recently become apparent that the radiotoxicity of Auger electrons is caused mainly (~90%) by an indirect mechanism(s) (*16–19*). These findings also constitute a radical shift in the understanding of the mechanisms underlying the radiotoxic effects of low-energy emitters.

The toxic effects of low-energy electron emitters had frequently been assumed to depend on the covalent binding of the Auger electron-emitting radionuclide to nuclear DNA (*20–24*). Several investigators (*25–29*), however, have shown that various agents (e.g., steroids, growth factors, and DNA intercalators) radiolabeled with such isotopes are also highly toxic to mammalian cells (exponential decrease in survival). These reports expand the portfolio of agents and approaches that can be used to target Auger electron-emitting radionuclides to tumor cells.

The toxicity and therapeutic potential of low-energy electron emitters had been thought to require the radiotargeting of each and every tumor cell (a direct consequence of the short range of the emitted electrons and therefore the absence of "cross-fire" irradiation of neighboring cells). This notion, too, has proven to be inaccurate, as the decay of such isotopes has recently been shown to lead to a "bystander effect," an in vivo, dose-independent inhibition or retardation of tumor growth in nonradiotargeted cells by a signal(s) produced in Auger electron-labeled cells (*30*). These in vivo findings should also have a dramatic impact on risk assessment after the administration of radiopharmaceuticals (all of which emit low-energy electrons) to patients, especially because dose estimations are traditionally performed by averaging the radiation dose to cells within a tissue or organ from radioactive atoms present on or within the cells (self-dose) and that from radionuclides present in or on other cells or in the extracellular fluids (cross-dose). Such radiation-absorbed dose estimates have always played an important role in determining the amount

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of radioactivity to be administered to patients in diagnostic or therapeutic procedures as well as in assessing environmental radiation risks, for example, radon inhalation. When a bystander effect is factored in, the actual radiobiologic response will be greater than that predicted by dosimetric estimates alone.

Most studies assessing the therapeutic efficacy of low-energy electron emitters were performed with the thymidine analog 5-iodo-2′-deoxyuridine (*31–33*). In these studies, in which such DNA-incorporated Auger electron emitters were shown to be therapeutically very efficacious (4- to 6-log kill of tumor cells), the underlying assumption was the need to bring the Auger electron emitter into the cell nucleus and bind it covalently to DNA. Additional studies (*34–43*) have invalidated the above assumption and established that for some carrier molecules internalized into the nuclei of tumor cells, covalent DNA binding is not necessary for toxicity and, consequently, that such molecules are potentially useful as carriers of Auger electron-emitting radionuclides and can be used in cancer therapy.

The article by Chen et al. (*44*) in this issue of *The Journal of Nuclear Medicine* is an excellent example of the use of an agent that is transferred to the nucleus but not covalently bound to DNA. The authors of this study examined the efficacy of ^{111}In-labeled diethylenetriaminepentaacetic acid–human epidermal growth factor (^{111}In-DTPA-hEGF) for the treatment of breast tumors that overexpress the epidermal growth factor receptor (EGFR). In essence, mice were implanted subcutaneously with either EGFR-overexpressing tumor cells or tumor cells expressing a low level of EGFR and injected later with ^{111}In-DTPA-hEGF, and the biodistribution and therapeutic efficacy of the radiopharmaceutical were determined.

This is a novel approach that relies on earlier results in which Reilly et al. (*27*) had demonstrated high and selective in vitro toxicity of ^{111}In-DTPA-hEGF in EGFR-overexpressing breast tumor cells and rapid internalization of the radionuclide into the cytoplasm of tumor cells, with a proportion of the internalized ^{111}In being present within the nuclei of these cells. The current article reports that the administration of ^{111}In-DTPA-hEGF to mice bearing EGFR-overexpressing breast tumors leads to tumor size–dependent uptake (for tumors of 1–2 mg, >80% of the injected dose per gram; for tumors of 6–30 mg, ~5% of the injected dose per gram), a 3-fold decrease in the rate of growth of "large" (15 mm^3) tumors and, most interesting, a profound regression of "small" (10 mm^3) tumors. Specifically, these data suggest that this radiopharmaceutical (and other Auger electron-emitting therapeutic agents) may be most valuable in the treatment of small-volume breast cancer metastases, support the hypothesis purporting the appropriateness of carrier molecules that enable the intranuclear localization of Auger electron emitters, and provide the impetus needed for the development of other low-energy, electron emitter carriers in the fight against cancer.

It is clear that radiopharmaceuticals labeled with low-energy electron emitters will play a role as radiotherapeutic agents in the near future. The foundations for this optimism are the high toxicity and therapeutic efficacies reported; the ready availability of many no-carrier, low-energy, electron-emitting radionuclides with variable physical half-lives and known chemical properties; the low autoradiolysis of such radiopharmaceuticals (even at high specific activities); and the emission by many of these radionuclides of γ-photons, which are suitable for imaging and as such will enable the rapid selection of radiopharmaceuticals with appropriate radiotargeting pharmacokinetics.

To paraphrase Regaud and Lacassagne (*45*), "the ideal agent for cancer therapy would consist of heavy elements capable of emitting radiations of molecular dimensions, which could be administered to the organism and selectively fixed in the protoplasm of cells one seeks to destroy. Although this is perhaps not impossible to achieve, the attempts so far have been unsuccessful." Certainly, the hope of these two pioneers will soon be achieved.

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