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Drug-Mediated Image-Guided Radiotherapy—Mining for the Mother Lode

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The therapeutic nugget desired of anticancer agents is not to restore normal biologic processes in cancer cells but rather is to kill them. Non-selective cytotoxic agents inherently strike against cancer cells, but also make collateral adverse effects in healthy cells a major health concern. In this way, non-selective cytotoxic agents might be considered 'fools gold' to some. However, targeted anticancer agents have made the prospect of striking against specific biomolecular differences between cancer cells and healthy cells an attractive therapeutic strategy. For instance, a new potent ribonucleotide reductase inhibitor has been mined for its claim of accentuating radiation and chemotherapy effects with clinical benefit [1,2].What if this or other novel biological therapeutic could serve as imaging agents used to discriminate cancer cells from healthy cells in a better way?

Here, the radio chemotherapeutic management of advanced stage cervical cancer provides a meaningful illustrative example. Cervical cancers over express ribonucleotide reductase [3], a ubiquitous rate-limiting enzyme responsible for the de novo generation of the building blocks of DNA. Healthy cervix cells have less expression of ribonucleotide reductase [4]. Envision a biologic anti cancer agent that nestles around an iron-stabilized radical in the ribonucleotide reductase enzyme and disrupts the vital proton-coupled electron transfer of its radical to its active site [5,6]. When radiation and chemotherapy damage DNA, and thus increase the demand for DNA building blocks, a blocked ribonucleotide reductase cannot provide the demanded supply of DNA precursors and cells die [1]. Clinically, the targeting of ribonucleotide reductase by such a potent inhibitor during radio chemotherapy has found success [2]. The eureka! Moment might be just that there is more to learn from this interesting drug-mediated therapeutic pharmacology.

There is a rich history of cancer-directed radiation therapy guided by 2-[18F] fluoro-2-deoxy-D-glucose Positron Emission Tomography (PET) images superimposed upon computed tomography radiation planning images [7-9]. But, PET images do not necessarily distinguish between cancer cells or immune cells rapidly dividing. Could an anticancer agent like a ribonucleotide reductase inhibitor be a more discriminatory nuclear imaging agent? APET-compatible, labeled ribonucleotide reductase inhibitor, that has desirable properties of target specificity and of short circulation time, could fill this role. The overarching idea is to mark cancer cell bearing tissue using a labeled ribonucleotide reductase inhibitor, overlay mined drug-mediated PET images and radiation therapy planning images, irradiate cancer-bearing tissue precisely, and thus eradicate cancer cells.

New cancer research strategies have focused on the clinical development of targeted biologic agents that aim to accentuate cancer cell kill. Clinical development of labeled targeted biological agents might also prove 'golden' in the setting of drug-mediated image-guided radiotherapy. Future study is warranted.

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