Editorial

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Alpha particles irradiation: a paradigm change in cancer brachytherapy

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Editorial

In a breakthrough development in brachytherapy, scientists Keisari and Kelson of Tel Aviv University, Israel have developed an alpha (α) particle irradiation scheme that could apparently zap both DNA strands of cancer cells with a success rate of approximately 70% and a shrinking rate of 100% of the remaining cancerous cells. This advance was made 15 years ago but remained largely unexploited since then. It has recently received a new impetus in terms of both its research and development, including clinical trials. To appreciate this paradigm change in cancer brachytherapy and its capabilities and import, the following nuclear radiation summary is initially provided.

All matter is composed of individual entities called *elements*. Each element is distinguishable from the others by the physical and chemical properties of its basic component – the *atom*. Each atom consists of a small central core, the *nucleus* (radius 10^{-14} m), where most of the atomic mass is located and a "cloud" of *electrons* moving in orbits (radius 10^{-10} m) around the nucleus. The properties of the atoms are derived from the constitution of their nuclei and the number and organization of the orbital electrons. The nucleus contains two kinds of fundamental particles: *protons* (positively electrically charged) and *neutrons* (no charge). The number of protons is equal to that of the electrons, making the atom electrically neutral. Thus represented, the atoms are also called *nuclides*. On the basis of different proportions of neutrons and protons in the nuclei, atoms have been classified into the following categories: *isotopes* (nuclei having the same numbers of protons but different numbers of neutrons), *isotones* (same numbers of neutrons but different numbers of protons), *isobars* (same total numbers of protons and neutrons), and *isomers* (same numbers of protons and neutrons). Certain combinations of neutrons and protons result more in stable (non-radioactive) nuclides than others.

There are two types of radiation (*electromagnetic* and *particle*), but only the latter will be of interest here. (Note: Following Louis de Broglie in his seminal 1924 thesis, these two types are alternative forms of the same radiation, that is either wave or particle.) The term *radiation* applies to the emission and propagation of energy through space or a material medium. By *particle radiation*, we mean energy propagated by traveling corpuscles that have a definite rest mass and within limits have a definite momentum and defined position at any instant. Besides neutrons, protons and electrons discussed earlier, many other atomic and subatomic particles have been discovered. These particles can travel with high speeds, depending on their kinetic energy, but can never attain exactly the speed of light in vacuum. Also, they interact with matter and produce varying degrees of energy transfer to the medium.

Radioactivity was first discovered by Henri Becquerel in 1896. It is a phenomenon in which radiation is given off by the nuclei of the elements in the form of either particles (α, β, γ) or electromagnetic radiation or both: α-particles (helium nuclei) are electrically positively charged, β-particles are negatively charged with the former being heavier than the latter. On the other hand, γ-particles have no charge and are similar to x-rays except for their nuclear origin. The particles inside the nucleus (neutrons which have no charge and protons which have positive charges) possess kinetic energy which is, however, insufficient to allow them to overcome the electrical *potential barrier* that surrounds the nucleus to leave it. These internal nuclear particles are held together by electrostatic repulsive forces between particles of similar charge. However, the nature of the forces involved in keeping the integrity of the nucleus is quite Four nuclear forces have been recognized which, in the order of their decreasing strength, are: (a) the *strong* nuclear force (it is responsible for holding the nucleons together in the nucleus); (b) the *electromagnetic* force (a repulsive force that tends to disrupt the nucleus); (c) the *weak* nuclear force (it appears in certain radioactive decays, e.g., β-decay); and (d) the *gravitational* force (which is comparatively negligible).

Now, brachytherapy is a method of treatment in which sealed radioactive sources are used to deliver radiation at a short distance by interstitial, intracavitary, or surface application. With this mode of therapy, a high radiation dose can be delivered locally to a tumor with rapid dose fall-off in the surrounding normal tissue. In the past, brachytherapy was carried out mostly with radium or radon sources. Currently, use of artificially produced radionuclides is rapidly increasing. These redionucleides include: cesium Cs-137 (a γ-ray emitting radioisotope that is used as a radium substitute in both interstitial and intracavitary brachytherapy); iridium I-192 (a lower energy source that requires less shielding for personnel protection); gold Au-198, (used in the same way as radon seeds have been employed for permanent interstitial implants); iodine I-125 (for permanent implants with a long, 60.2 days half-life that is convenient for storage and low photon energy which requires less shielding); and palladium Pd-103 (with a shorter half-life of 17 days than that of I-125, it may provide a biological advantage in permanent implants as the dose is delivered at a much higher rate). (Note: cobalt Co-60 is rarely used now in brachytherapy). New technical developments have stimulated increased interest in brachytherapy. These include: the introduction of artificial isotopes, afterloading devices to reduce personnel exposure, and automatic devices with remote control to deliver controlled radiation exposure from high radioactivity sources. Although electrons are often used as an alternative to interstitial implants, brachytherapy continues to remain an important mode of therapy, either alone or combined with external beam therapy.

Radium has two isotopes: radium-226 with a half-life (the time after which it has lost 50% of its radioactivity) of 1600 years and radium-222 with a half-life of 3.83 days. It is this latter isotope that is of interest here. Its α-radiation travels at somewhat less than two microns (1/20th of a millimeter) inside human tissue so that treating a tumor of, say, 5 cm would require an inordinate amount (hundreds of thousands of α-particles) – a seeming impossibility. However, using the isotope radium-222, Keisari and Kelson discovered that its α-radiation can travel as far as 3 mm. It also releases atoms that diffuse inside a tumor and then emit their own α-radiation (a cascading effect), requiring far fewer α-particles to kill a tumor. This is the only instance where α-radiation is used, all other brachytherapy approaches using β- or γ-radiation. These other radiations cause only DNA's single strand breaks from which the cell can recover and it is not focused, causing a lot of side effects and destroying adjacent healthy tissue. When the healthy tissue around the tumor is not destroyed along with the cancer, the immune system is stimulated to recognize and attack the same type of tumors elsewhere in the body – these are metastases that are the cause of death for 85% of cancer patients. Of particular note, leakage of radon gas from a radium source represents a significant hazard if the source is broken. The sources, however, are doubly encapsulated to prevent such an occurrence. Spontaneous rupture of a sealed radium source due to pressure build-up of helium gas (from α-particle disintegrations) is considered unlikely.[1–9]

The use of α-radiation has tremendous value not only in destroying the tumor but additionally preventing cancer from spreading to other organs. Thousands of animal studies have been done, and the first human clinical trials have been conducted in Israel, Italy, New York and Montreal for congenital melanocytic nevus. These trials have shown that ~ 70% of the tumors have been entirely eliminated and, of the rest, 100% have been shrunk so that it will be easier to more easily surgically excise them. Clinical trials are planned in 2019 in France, Montreal and New York (pancreatic and prostate cancer), Russia (breast cancer) and Israel (prostate cancer). Additional trials are planned to be later initiated for more than 20 other indications – such as vulvar, cervical, renal and colon cancer – at medical centers in more than 25 countries. Apparently, any kind of solid tumor could thus be treated, including currently incurable cancers such as, hopefully, pancreatic cancer.

Despite the power of α-radiation, it is actually safer than conventional β- or γ-treatments because it uses less radioactivity for the same effect. Also, treatment kits can be shipped to hospitals almost in regular boxes and patients can be treated in an outpatient setting with no radioactive shielding as its radioactivity would have diminished to 50% of its initial value in 3.83 days (25% in 7.76 days; 12.5% in 11.49 days; 6.25% in 15.32 days, etc.). While very helpful, this short half-life my also pose some difficulties. The time window between the shipment of the kit and its administration to a patient is short and critical for most if not all potency may be lost. This may require the installation of production facilities close to the main cancer treatment centers. The first such facility is already operational in Israel. A second facility has been approved in Massachusetts, a third in Japan and a fourth in Europe. Approvals are expected in 2020 for the European Union and 2022 for other sites in the U.S. and Japan. Radiation oncologists are eagerly waiting the results of these clinical trials with an eye to their prompt applications for patient treatments.

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