

Therapy with Alpha Rays

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Treatment with radioactive isotopes has been the first clinical application of Nuclear Medicine, when, in the early '40s, the Phosphorus-32 was used for polycythemia and some forms of leukemia^{1,2}, and subsequently the administration of iodine-131 was adopted for the therapy of thyroid disease^{2,3}.

Since that time, Nuclear Medicine therapy, also before known as radiometabolic, has come a long and successful road, with the synthesis of many classes of radiopharmaceuticals, from those receptorial⁴ to monoclonal antibodies^{5,6}, to various molecular probes. Moreover the identification of other radionuclides than Iodine-131 and the infamous Gold-198, used for radiosynoviorthesis⁷, has contributed to the development of therapeutic branch of Nuclear Medicine. Then entered into clinical practice emitting beta particles, electrons, with physical characteristics very advantageous, as Samarium-153⁸ or Yttrium-90⁹.

These isotopes can be administered both such or attached to some molecules that modify its selectivity in order to be distributed among the various tissues (carrier). Even the half-life of the radioisotope is important in defining the dose administered, as well as the radiosensitivity of the target.

The presence, moreover, of a contemporary gamma emission by the nuclide utilized also allows the execution of scintigraphic investigations after its administration, useful for monitoring the distribution of the radiopharmaceutical in the body and make the most of the time a predictive estimation of the dose received from the target compared to the administered activity¹⁰.

The small distance covered by corpuscular radiation emitted by utilized isotopes helps to make a more targeted treatment and, since all the radiated energy is released in a small space, thus irradiated cells cannot repair the damage that their DNA have suffered, then running into death.

For these reasons, Nuclear Medicine treatment presents a very low risk, for example, to cause the onset of cancer in treated subjects, so that often these therapies are also used for non-oncological diseases (such as hyperthyroidism, as mentioned before).

Calculate the amount of radiation absorbed by body tissues is critical for the success of the treatment¹¹. The objective is to estimate the dose to be administered to the patient as to provide maximum therapeutic effect but at the same time limit excessive irradiation of healthy tissues (especially the bone marrow and kidneys).

The clinical interest towards alpha emitters in Nuclear Medicine therapy, derives from the fact that with these nuclides it is possible to easily delete individual cancer cells, while this is not generally possible with beta emitters, while maintaining an acceptable toxicity profile.

In fact alpha particles emitting drugs have a higher BED of the most energetic beta particles, thus allowing more targeted treatments.

The simple physical basis of the difference between alpha and beta rays is the ratio of their masses, that is about 8000 to 1. This enormous difference, together with the electric charge, greater however only of a factor of 2, and energy emissions, higher only by a factor of 10, implies that alpha particles travel with non-relativistic speed (about 1/20 of the speed of light), while beta ones have a speed practically equal to the light speed

The slower speed of the alpha radiation therefore results in a much shorter route than that of the electrons in the middle traversed, thus resulting in a Linear Energy Transfer (LET) much higher, measured in keV/micron.

The 5.9 MeV and 8.4 MeV alpha LET are 80keV/micron and 61 keV/micron, respectively, while those of beta of 100 and 500 keV are 0.2 and 0.5 keV/micron.

This much higher LET generate ionization density along the path much higher and a much shorter range of route of the alpha particles, compared to beta ones. Both characteristics have very important implications for radionuclide therapy and dosimetry. The ionization density has a strong influence on the shape of the survival curve as a function of the dose.

Low LET radiation (photons and electrons) induces 3-9 ionizations on a distance of 3 nanometers. The alpha particle has such a short route that few cell diameters, typically 5, are crossed by each particle. The concentration of ionizations along the alpha route is so high that a single shot to the DNA is able to kill a single cell.

It is clear that in the case of beta rays, the mean dose concept is significant, even if considered on a macroscopic volume that can be small like a voxel of medical application scanners (the side of a few millimeters).

The concept of average dose is not significant however, with alpha rays, or, rather, slightly predictive of biological effects, because the same amount of energy deposited by a projectile directed to the cell membrane could give completely different biological effects to the cytoplasm or inside the nucleus .

The first clinical applications of alpha emitters are of very recent date and relate to the use of Radium-223 for the treatment of bone metastases¹². In fact, the Radium-223 behaves in nature as a mimetic of calcium, and then reaches, once administered, the bone lesions with higher calcium turnover. In this case the therapeutic effect, in addition to causing a net reduction in the painful symptoms, also demonstrated a significant increase in survival, on average estimated at 3.6 months. The aforementioned short route alpha leaves also unharmed neighboring tissues, particularly the bone marrow.

Other alpha emitters in study are the Bismuth-212 (synthesizable with a 244Ra / 212Bi generator) which, as its isotope Bismuth-213, can be chelated into special carrier¹³. Another nuclide is Astatine-211 which, similar to iodine, can bind a covalent bond to carbon atoms of other molecules¹³.

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