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Nuclear medicine perspective on radioimmunotherapy

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Radioimmunotherapy is a new type of therapy that targets radiation to the tumor using monoclonal antibodies (MAbs). The use of radiolabeled MAbs as a potential cancer treatment was first explored in the '50s. Only in the '70s, however, technological advancements allowed for the design and production of monoclonal antibodies directed against specific cellular antigens. The feasibility of combining a monoclonal antibodies directed against specific tumor-associated antigens with a radioisotope in order to deliver a therapeutic dose of radiation to a tumor cell has been studied since the early '80s. The safety and efficacy of radioimmunotherapy have been evaluated in clinical trials in patients with cancer. Several radioisotopes have been suggested as radiation source for radioimmunotherapy, including Yttrium, Lutetium and Iodine. At present most treatment uses the radioactive metal Yttrium-90, which delivers higher levels of local radiation to the tumor. The radiolabeled MAb is administered through a vein and then circulates through the body to the surface of tumor cells. The tumor cells are then destroyed by the radiation given off from the localized radiolabeled antibodies. A number of different antibodies have been studied over the last years to evaluate the potential clinical usefulness. Among the most known is carcinoembryonic antigen (CEA), a tumor antigen found in patients with breast, colon, lung, thyroid and ovarian cancers. Despite many efforts the results of radioimmunotherapy with antiCEA were not satisfactorily, and this approach is still under investigation.

Another sort of monoclonal antibodies were found more suitable for radioimmunotherapy, namely Mabs directed to some CD antigens, which are located on the surface of certain lymphomas. In fact some B-cell lymphomas arise from mature B-cells, and during this maturation process, they express on their surface antigens that are both unique to B-cells and also unique to this level of maturation. These antigens, such as CD-20 and CD-22, appear and then disappear: therefore these antigens can be used as targets. Therefore during the '90s clinical trials started to evaluate the effectiveness of radioimmunotherapy using anti-CD20 and anti-CD-22 monoclonal antibody conjugated to beta emitter isotopes, and a couple of treatment have reached FDA approval. Radioimmunotherapy has relevant potential advantages of in the treatment of patients with non-Hodgkin's lymphoma (NHL). In fact radioimmunotherapy affects normal cells that express the antigen that it is directed against or are in close proximity to antigen-positive tumor cells. The beta emission from radioimmunotherapy induces cellular damage through the formation of free radicals in the target and neighboring cells. Results of anti CD-20 radioimmunotherapy in term of overall response rate were very good, and it is likely that within the next few years, radioimmunotherapy will become part of the standard therapies offered to these patients.

In Europe the only approved radioimmunotherapeutic agent is currently Zevalin® (ibritumomab tiuxetan). Zevalin is an immunoconjugate in which the monoclonal antibody Ibritumomab is covalently bound to tiuxetan, a high-affinity, linker-chelator for the radioisotopes Yttrium-90 or Indium-111. The antibody moiety of Zevalin is Ibritumomab, a murine IgG1 kappa monoclonal antibody directed against the CD20 antigen, which is found on the surface of normal and malignant B lymphocytes. The tiuxetan chelator provides a stable linkage between the antibody and the radioisotope, permitting radiation to be directed against antigen-positive cells. The Yttrium-90 isotope is extremely useful, as it is a pure beta emitter with a physical half-life of 64.1 hours. In soft tissue, 90% of the energy emitted by the radioisotope is absorbed within a mean pathlength of 5 mm, corresponding to a distance of 100 to 200 cell diameters.

By the nuclear medicine point of view, Zevalin is a radiopharmaceutical quite easy to label and handle. Zevalin comes as a cold kit to be labelled with Yttrium-90: labelling procedures do not require heating and in our experience efficiency is very high, always > 95%. Pure beta emission of Yttrium-90 is a clear advantage regarding dosimetry and makes it possible to not isolate patients during treatment. Of course radioimmunotherapy with Zevalin requires a multidisciplinary approach, with a strong collaboration between specialists, including nuclear medicine, hematology, and health physics.