Recent Advances in Immunoscintigraphy and Radioimmunotherapy

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1. Immunoscintigraphy
Immunoscintigraphy, since its first clinical applications nearly 20 years ago, mainly in oncology, has demonstrated its diagnostic efficiency in well-defined indications (detection of occult recurrences in the abdomen and pelvis), but has not yet found its place in routine practice relative to conventional imaging methods. This apparent paradox is attributable to certain methodological limitations responsible for tumor-to-normal tissue ratios that are often inadequate for reproducible interpretation of images, and to the difficulty of repeating scans because of the immunogenicity of the murine antibodies used.

Technological advances in recent years in antibody engineering and the chemistry of chelating agents have made it possible to obtain short (Fab) or very short (scFv) fragments. In clinical studies, these fragments have been labeled with technetium-99m. They have rapid kinetics and provide an interpretable image a few hours after injection. The use of these relatively nonimmunogenic short fragments and of recently available human antibodies allows immunoscintigraphy to be repeated in the same patient. However, despite this technological progress, tumor-to-normal tissue ratios are still sometimes moderate or even poor, in which case image contrast is inadequate to allow easy interpretation. As a result, the reproducibility of intra- and interobserver interpretation is not optimal. For this reason, immunoscintigraphy is often considered as a difficult examination requiring solid experience for its interpretation. This situation explains in part why its routine use is limited, despite the availability on the market of several antibodies officially approved in the United States and Europe.

Two-step targeting techniques using the avidin-biotin system or the bispecific antibody-bivalent hapten system have allowed a significant reduction in the radioactive concentration of normal tissues for a tumor uptake equivalent to that obtained with directly labeled immunoconjugates. The result is a 3- to 6-fold increase in tumor-to-normal tissue ratios, which greatly facilitates image interpretation. It is thus possible to clearly visualize occult recurrences not visible with conventional imaging techniques.

The future of immunoscintigraphy is unlikely to concern the staging of certain primary tumors or even the early detection, with few exceptions, of recurrences of some types of cancer. It is probable that the joint use of $^{18}$FDG (fluorodeoxyglucose) and PET cameras dedicated to oncology, or SPECT cameras with systems of positron coincidence detection, is going to develop and become a reference technique because of the remarkable efficiency obtained, which is often superior to that of immunoscintigraphy (for example, in the visualization of recurrences of colorectal cancer). In these conditions, it is likely that, in the future, immunoscintigraphy will serve as a preliminary step before radioimmunotherapy in order to assess the level of radioimmunoconjugate uptake by the tumor target(s) and estimate the irradiation dose delivered to the tumor(s) and normal tissues.
2. Radioimmunotherapy

Many phase I/II clinical trials have been conducted using antibodies of various types, most often labeled with iodine-131.

Positive and even sometimes impressive results have been obtained with anti-CD20, anti-CD37 and anti-HLA-DR antibodies in cases of lymphomas refractory to chemotherapy. With anti-CD20 antibody (B1), the best results have been obtained with myeloablative activities (more than 80% complete responses), though quite appreciable results (nearly 50% complete responses) have also been obtained with non-myeloablative activities. Phase III trials are in progress to confirm the clinical advantage of this new therapeutic approach. The good results for tumor targets, sometimes of large size, may be explained by the known radiosensitivity of lymphomas and probably by the synergic action of low-dose irradiation and the biological activity native to the antibody used.

Very favorable results have also been obtained recently with murine and humanized anti-CD33 and anti-CD45 antibodies labeled with iodine-131 and associated with chemotherapy in the context of intensification therapy prior to a bone marrow transplantation in patients with myeloid leukemia.

In cases of solid tumor, the efficiency of these antibodies has been much more modest and even generally negligible. The main reason for this failure is that the tumors studied in most phase I trials were not very radiosensitive, and especially macroscopic and often large in size. As a result, tumor uptake of radioimmunoconjugates was relatively low (<0.01%/g), leading to dosimetric estimations inadequate for tumoricidal action (i.e. less than 30 Gy). In the relatively few cases of small tumor targets studied (i.e. weighing less than 5 g), tumor uptake was much greater (sometimes >0.1%/g), leading to dosimetric estimations above 100 Gy and thus probably tumoricidal. To date, toxicity in phase I trials has been mainly hematologic.

Several approaches for the optimization of radioimmunotherapy have been considered and are now under clinical validation. They seek to increase the tumor uptake of radioimmunoconjugates, lengthen the retention time of tumor radioactivity, reduce the concentration and retention time of radioactivity in normal tissues, and decrease the immunogenicity of radioimmunoconjugates in order to allow their repeated injection in the same patient.

Two-step targeting techniques, which consist first in injecting a non-radiolabeled immunoconjugate and then, a few days later, injecting a radiolabeled molecule which is taken up by the immunoconjugate prelocalized into the tumor target(s), have led to a significant reduction in the radioactivity of normal tissues without decreasing tumor uptake. Techniques using the avidin-biotin system and the bispecific antibody-bivalent hapten system are currently undergoing preclinical validation in the animal and clinical validation in patients. The first results tend to confirm their advantage over conventional techniques using directly radiolabeled antibodies. Moreover, there is a tendency to replace murine antibodies with humanized or human antibodies which produce significantly reduced immunogenicity.

Finally, it is noteworthy that the size of tumor targets is a determinant parameter for the efficiency of radioimmunotherapy. It seems illusory to expect curative efficacy for macroscopic tumors other than radiosensitive ones. The clinical target of radioimmunotherapy for curative purposes will consist of microscopic tumors disseminated within the body.