Which radionuclides will nuclear oncology need tomorrow?

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Current situation

The role of nuclear medicine in oncology has changed dramatically in recent years owing to outstanding technical advances in imaging and therapy. This progress is opening up new, exciting perspectives which should ensure that nuclear medicine techniques will become standard diagnostic and therapeutic modalities, complementing conventional modalities. Positron emission tomography/computed tomography (PET/CT) technology with ^{18}F-fluorodeoxyglucose (FDG), which has been developed clinically in less than 10 years, is now accepted as the gold standard in oncological imaging [1]. Moreover, a number of other fluorinated radiopharmaceuticals are being evaluated for their ability to complement FDG [2], and some could be approved for routine clinical use in the future.

For nearly 50 years, radionuclide therapy was limited to the treatment of differentiated thyroid cancer. From the 1970s onwards it was then extended to a few therapeutic "niches", with the use of ^{131}I-MIBG in some neuroendocrine tumours and of bone-seeking radiopharmaceuticals in the palliative treatment of painful bone metastases of prostate cancer. Over the past 10 years these limited applications have been rapidly extended to a larger panel of malignant tumours owing to the availability of new carriers, including monoclonal antibodies (MAbs) and peptides, new targeting methods, including pretargeting, and new radionuclides, including ^{177}Lu and ^{90}Y.

The efficacy of radioimmunotherapy (RAIT) was first documented with anti-CD20 MAbs labelled with ^{131}I (Bexxar) and ^{90}Y (Zevalin), which have been approved in the USA (both Bexxar and Zevalin) and in Europe (Zevalin only) for the treatment of follicular, indolent and transformed, non-Hodgkin's lymphoma. Despite the documented superior efficacy of Zevalin as compared with rituximab in terms of objective response rates, some haematologists have been disappointed by the fact that the time to progression (TTP) was found not to be significantly longer with Zevalin than with rituximab, although the trial was only powered to detect a 25% difference in overall response rates. However, a trend towards a longer TTP was observed in patients achieving a complete/unconfirmed complete response (p=0.07), despite the fact that many of the treated patients were at high risk (elderly, heavily pre-treated or with bulky disease) [3].

In the near future, a very promising new application of Zevalin will be its use as consolidation therapy after combination chemotherapy and rituximab to treat minimal residual disease, which corresponds to the optimal indication for RAIT. Interestingly, a recent report on abbreviated chemotherapy followed by tositumomab (anti-CD20 MAb) and ^{131}I-labelled tositumomab (Bexxar), as consolidation therapy in untreated patients, showed that median progression-free survival had not been reached after a median follow-up of 58 months. The 5-year estimated progression-free survival rate was 60% [4]. A similar randomised study has been performed in 414 patients to compare Zevalin and no treatment as consolidation after chemotherapy and rituximab therapy [5]. The enrolment was completed at the beginning of 2005 and the results will be known in 2007, with the hope of a longer TTP in the patients treated by Zevalin. Thus, RAIT in patients with follicular non-Hodgkin's lymphoma appears to be a new, efficient treatment modality to complement chemotherapy and immunotherapy.

RAIT and radiopeptide therapy of solid tumours, which are relatively radioresistant, face more challenging problems. No real efficacy was documented in the past 10 years until recent reports showing some moderate efficacy owing to higher injected activities, technological improvements (pretargeting or new radionuclides) and more favourable clinical targets (smaller tumours). Radiopeptide therapy, using ^{177}Lu-octreotate, has proved to be more efficient than chemotherapy in patients with neuroendocrine tumours [6]. The duration of response was longer than 36 months, as compared to 3–20 months with chemotherapy [7–9].

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In a phase II clinical study of RAIT using a humanised anti-carcinoembryonic antigen (CEA) antibody (labetuzumab) directly labelled with ^{131}I in patients with colorectal carcinoma after salvage resection of liver metastases, a better than predicted outcome was observed: the survival rate was 51% at 5 years, as compared with the expected rate of 28% derived from an analysis of 1,596 patients [10]. This quite encouraging result was obtained in the most favourable clinical setting of occult or microscopic residual disease. It must be confirmed in a large, randomised, prospective study.

Pretargeted RAIT (pRAIT) has led to improved survival in patients with high-risk medullary thyroid carcinoma [11]. pRAIT against CEA induced long-term disease stabilisation and a significantly longer survival in high-risk patients with a calcitonin doubling time shorter than 2 years, compared with similar high-risk, untreated patients. To our knowledge, this is the first report of long-term efficacy in terms of a survival benefit of RAIT in patients with solid tumours and confirmed metastatic disease.

Finally, intracavitary injection of ^{131}I-labelled anti-tenascin MAb combined with chemotherapy in patients with recurrent malignant glioma has shown encouraging results, with a median survival greater than that of historical controls treated with surgery plus ^{125}I brachytherapy [12].

More generally, there is a consensus that optimal clinical efficacy of targeted radionuclide therapy will be achieved in combination with chemotherapy/biotherapy in patients with small disseminated tumours.

Future prospects

Given these encouraging diagnostic and therapeutic results, what progress can be expected in the coming years?

FDG-PET has progressively asserted itself as the gold standard of imaging in oncology for early tumour detection and assessment of response to treatment. However, FDG is taken up in any lesion that needs a source of energy for its own metabolism, including inflammatory processes. Such non-specific uptake results in a limited diagnostic specificity of FDG-PET. The use of antibodies, specific for a variety of tumour-associated antigens, could greatly improve the diagnostic specificity of PET. This new approach, termed immuno-PET, is being evaluated in preclinical studies using different forms of several antibodies. The first results confirmed a higher specificity of immuno-PET as compared with FDG-PET [13, 14]. However, labelling of immunoconjugates with ^{18}F is less than ideal because its short half-life is not compatible with the time necessary for optimal tumour targeting. Consequently, there is a need for innovative positron-emitting radionuclides with half-lives longer than 10 h.

The future of radionuclide therapy will require the injection of higher activities to reach efficient absorbed doses in radioresistant solid tumours, while limiting the irradiation of vital organs. To achieve this, it will be necessary to evaluate, as accurately as possible, the dose delivered to these organs (e.g. liver, lung and kidney) by pre-therapeutic dosimetry studies, using PET rather than single-photon emission computed tomography to take advantage of its more accurate quantification. Some pairs of beta+/beta− emitting radionuclides will be available, including ^{124}I/ ^{131}I, ^{86}Y/ ^{90}Y and ^{64}Cu/ ^{67}Cu.

^{131}I is used in several therapeutic applications, including the treatment of thyroid cancers, but its strong gamma emission requires patient isolation in shielded rooms in many countries. Thus, radionuclides without gamma emission or emitting gammas of lower energy, such as the reactor-produced ^{90}Y and ^{177}Lu, are preferred. ^{67}Cu has also been proposed as an interesting option and, in a clinical study comparing ^{131}I, ^{90}Y and ^{67}Cu, therapeutic indexes were found to be markedly higher with ^{67}Cu, except for the liver [15]. It has also been suggested that radionuclides with lower beta energy, and thus a lower toxicity range, such as ^{67}Cu and ^{177}Lu, are better suited for the treatment of small tumour lesions, which are also those that are treated with some success by targeted radionuclide therapy [16].

Another promising approach will be the use of alpha particle-emitting radionuclides to take advantage of the high tumour cytocidal effect of alpha particles as compared with that of beta particles. These radionuclides are also considered best suited to kill isolated tumour cells and microscopic disease owing to their very short track of energy deposition. However, experience in targeted therapy of cancer with these radionuclides remains quite limited, with only a few, scarcely available, radionuclides (^{212}Bi, ^{213}Bi, ^{211}At and possibly ^{212}Pb or ^{149}Tb) [17].

Short-term availability of innovative radionuclides

In the context of rapidly growing nuclear oncology and the resulting need for innovative radionuclides, a high-energy (70 MeV), high-intensity (750 μA) cyclotron with proton and alpha beams, called ARRONAX[1] (Accelerator for Research in Radiochemistry and Oncology in Nantes Atlantic), will be operating in Nantes, France, in the last quarter of 2008. As a part of this endeavour, a survey was performed in 2005 to evaluate the expectations of European researchers in terms of innovative radionuclides. A questionnaire was sent to 134 nuclear medicine centres in Europe. Fifty-four answers (40%) were received from 11 countries (Austria, Belgium, France, Germany, Great Britain, Italy, The Netherlands, Poland, Romania, Spain and Switzerland).

Analysis of these answers (Fig. 1) shows that four positron-emitting radionuclides were considered of strong interest in the near future: ^{124}I, ^{68}Ga, ^{86}Y and ^{64}Cu. ^{68}Ga can be made available daily for 1 year from a ^{68}Ge/ ^{68}Ga generator (half-life 270.8 days). However, the short half-life of ^{68}Ga (68 min) limits its use to the labelling of rapidly diffusible carriers, such as peptides. The three other

[1] The name ARRONAX also refers to Professor Aronnax, a character in the novel *Twenty Thousand Leagues Under the Sea* by the famous French writer Jules Verne, who was born in Nantes in 1828.

radionuclides can be used in pre-therapeutic PET for the evaluation of normal organ (liver, kidney, lung) dosimetry before injection of their beta-emitting counterparts (^{131}I,^{67}Cu and ^{90}Y). It should be noted that ^{86}Y emits non-negligible percentages of high-energy gamma rays, resulting in a relatively high exposure rate and thus requiring some specific radiation safety procedures.

For therapeutic applications, two radionuclides were favoured:^{67}Cu and ^{211}At (Fig. 1). Only a few clinical studies have been performed with^{67}Cu (half-life 2.58 days) owing to limitations on its production (need for high proton energy and small cross-section). Nevertheless, the radiophysical characteristics of this radionuclide fit well with its use in radionuclide therapy. ^{211}At appears to be the radionuclide of choice for alpha-therapy, even if the first clinical phase I alpha-immunotherapy was performed with a^{213}Bi-labelled antibody [18]. Indeed,^{225}Ac/^{213}Bi generators may be prepared from^{229}Th, but the supply is limited. A cyclotron could be used, but this would require a radioactive^{226}Ra target, which imposes severe technical constraints. In addition, the half-life of^{213}Bi (46 min) is too short to conform to the pharmacokinetics of antibodies. The longer half-life of ^{211}At (7.2 h) is more appropriate for this application.

Conclusion

Nuclear oncology will continue to see the development of PET and PET/CT, and targeted radionuclide therapy is coming of age. Comparatively, the use of single-photon emitting radionuclides for diagnosis will probably decline slowly in the absence of a technological breakthrough that would make single-photon scintigraphy more sensitive and more quantitative. A recent preclinical study with^{99m}Tc CEA pretargeting presents such a prospect [19], and needs to be confirmed clinically. Research needs a larger spectrum of radionuclides for diagnosis and therapy. Consequently, several radionuclides are in strong demand: positron emitters with a longer half-life that would foster immuno-PET and precise pre-therapeutic dosimetry (i.e.^{124}I,^{64}Cu and^{86}Y), as well as therapeutic beta-(^{67}Cu,^{177}Lu) or alpha- (^{211}At,^{213}Bi) emitters. The priorities of ARRONAX will include supporting the nuclear medicine research community by providing those radionuclides with current limited availability by means of efficient production using a high-energy, high-intensity cyclotron.

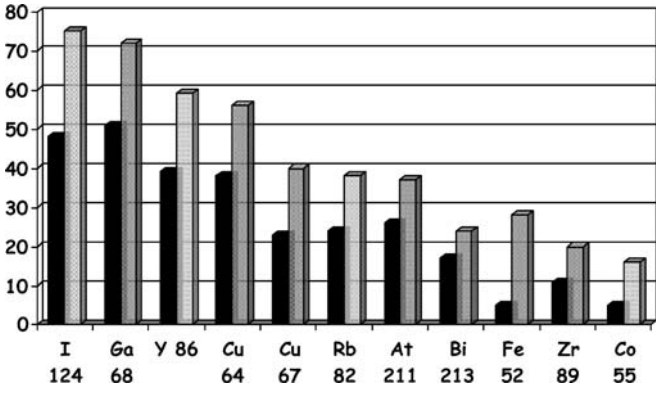

Fig. 1. Radionuclides classified as being of "very strong" (corresponding to +++ responses:*black bars*) or "strong" (corresponding to ++ or +++ responses:*hatched bars*) interest. Results are expressed as a percentage of responses to the questionnaire

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