

Practical implementation of clinical dosimetry on radionuclide therapy for thyroid cancer and neuroendocrinal tumours

M. Luster, Ulm (DE)

Although dosimetry has been of important value in the preclinical phase of radiopharmaceutical development, its clinical use to optimise the administered activity on an individual patient basis has been less evident. Recent developments in hybrid imaging, including micro-devices for animal research, and molecular medicine however stimulated the more widespread use of modern therapy and dosimetry techniques. Unfortunately, the lack of comprehensive clinical trials of radionuclide dosimetry in predicting therapy outcome has led to a general belief that dosimetry methods are logistically challenging and prone to a large degree of uncertainty. Data in the literature which underscore the potential of dosimetry to avoid under- and overdosing and to standardise radionuclide therapy methods are scarce but recently supportive evidence is increasing.

Adjuvant therapy of differentiated thyroid cancer with radioactive iodine is a standard procedure for the ablation remnant thyroid tissue following surgery and for the treatment of iodine avid metastases. In general radioiodine therapy has proven to be a safe and effective method.

The activity to be used for radioiodine therapy still remains subject to discussion. Usually patients are treated with standard activities reflecting the physician's rating of the highest safe or "adequate" dosage rather than with an optimized treatment activity based on prior measurement of the patient's individual biokinetics. Such a standard activity poses a risk of either under dosing the patient or of exceeding common safety limits. There is a broad range of fixed activities of I-131 recommended to be administered. In many cases, an activity between 1.1 and 3.7 GBq is prescribed for the first radioiodine therapy after thyroidectomy in newly diagnosed DTC to ablate the remaining glandular tissue. Higher amounts of I-131 are given in subsequent therapies or in case of metastatic disease. Normally, the activity is limited for safety reasons to around 7.4 GBq. The main disadvantage in using a fixed activity approach is the failure to consider the individuality of the patient. The "optimal" activity of radioiodine to treat metastatic thyroid carcinoma is the lowest possible amount of radioiodine that delivers a lethal dose of radiation to the entire lesion/metastasis while minimizing side effects. Empiric fixed activities by their very nature make no attempt to determine either the minimal radioiodine activity that will deliver a lethal dose or the maximum allowable reasonably safe absorbed dose. Patient-specific blood-based dosimetry is comparatively easy to perform before and during therapy. In selected patient cases this procedure will allow extending the activity beyond the limit of therapies using fixed activities and will reduce the risk of severe side-effects.

Presently there are two dosimetric concepts for the treatment of thyroid cancer using radioiodine: a) the bone marrow dose limited approach and b) lesion-based dosimetry. Both concepts and their clinical applications are described.

Recently, the European Association of Nuclear Medicine published a standard operational procedure for pre-therapeutic dosimetry in DTC patients incorporating a safety threshold of a 2 Gy absorbed dose to the blood.

In the case of lesion-based dosimetry the pre-therapeutic use of I-124 seems to be state of the art although the matter of stunning has not been settled. In addition, careful calibration of the PET(/CT) scanners is mandatory. In the lesion based approach the pre-therapeutic or therapeutic administration of I-131 does not take into account regional differences in the local iodine uptake.

Additionally there are a number of potential drawbacks of dosimetry that may preclude its use in many centres. One problem is the uncertainty of volume determinations by neck ultrasound shortly after thyroid surgery since the differentiation between scar tissue, haematoma and thyroid remnant is often difficult. The same holds true for the use of computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET) in the evaluation of distant metastatic lesions, especially in the case of diffuse lung metastases. Also, it remains difficult to predict radioiodine kinetics during therapy from prior diagnostic studies owing to the large difference in administered and measured activity and potential subsequent biological effects.

Treatment with radiolabeled somatostatin analogues, such as [90Y-DOTA0,Tyr3]-octreotide and [177Lu-DOTA0,Tyr3]-octreotate, is a promising new tool in the management of patients with inoperable or metastasized neuroendocrine tumors. Provided renal-protective agents are co-infused, toxicity is generally mild. Adequate dosimetry is mandatory for effective and safe peptide receptor radionuclide therapy (PRRT). Dosimetric and dose-escalating studies with [90Y-DOTA0,Tyr3]-octreotide, with and without renal protection showed no major acute reactions up to an administered activity of 5.55 GBq per cycle.

Besides the kidneys, the bone marrow is a potentially dose-limiting organ. The radiation dose to the bone marrow is usually calculated according to the MIRD scheme, where the accumulated activity in the bone marrow is calculated from the accumulated radioactivity of the radiopharmaceutical in the blood. Forrer et al. recently showed that after PRRT with [177Lu-DOTA0,Tyr3]octreotate, the radioactivity concentration in the bone marrow is identical to that in the blood while there is considerable variation in bone marrow absorbed dose between patients. The contribution of the cross-dose from source organs and tumours to the bone marrow dose appeared to be most relevant. The authors concluded that individual calculation of the bone marrow absorbed dose is mandatory.

The rationale for using a dosimetry-based approach is to replace the conventional fixed activity regimen by a modern setting which allows the administered therapeutic activity to be increased while avoiding undesired side effects. Using this strategy the absorbed dose to the cancerous or remnant tissue can be optimized without inducing potential toxicity.

This continuing education session is directed primarily towards nuclear technologists active or interested in diagnosis and treatment of these diseases. By getting an overview of the current state-of-the art and recent developments, this session seeks to provide a foundation to participants for refining their services in the future.

The participant will also be enabled to identify the major components needed for pre- and post-therapeutic dosimetry.

References

- Lassmann M, Hänscheid H, Chiesa C, Hindorf C, Flux G & Luster M. EANM Dosimetry Committee series on standard operational procedures for pre-therapeutic dosimetry I: blood and bone marrow dosimetry in differentiated thyroid cancer therapy. *Eur J Nucl Med Mol Imaging* 2008;35:1405-1412.
- Maxon HR, Thomas SR, Hertzberg VS, Kereiakes JG, Chen IW, Sperling MI & Saenger EL. Relation between effective radiation dose and outcome of radioiodine therapy for thyroid cancer. *N Engl J Med* 1983;309:937-941.
- Jentzen W, Hobbs RF, Stahl A, Knust J, Sgouros G & Bockisch A Pre-therapeutic (124)I PET(/CT) dosimetry confirms low average absorbed doses per administered (131)I activity to the salivary glands in radioiodine therapy of differentiated thyroid cancer. *Eur J Nucl Med Mol Imaging* 2010;37:884-895.
- Kolbert KS, Pentlow KS, Pearson JR, Sheikh A, Finn RD, Humm JL & Larson SM. Prediction of absorbed dose to normal organs in thyroid cancer patients treated with 131I by use of 124I PET and 3-dimensional internal dosimetry software. *J Nucl Med* 2007;48:143-149.
- Kulkarni K, Van Nostrand D, Atkins F, Aiken M, Burman K & Wartofsky L. The relative frequency in which empiric dosages of radioiodine would potentially over treat or under treat patients who have metastatic well-differentiated thyroid cancer. *Thyroid* 2006;16:1019-1023.
- Cremonesi M, Ferrari M, Zoboli S, Chinol M, Stabin MG, Orsi F, et al. Biokinetics and dosimetry in patients administered with (111)In-DOTA-Tyr(3)-octreotide: implications for internal radiotherapy with (90)Y-DOTATOC. *Eur J Nucl Med* 1999;26:877-886.
- Forrer F, Krenning EP, Kooij PP, Bernard BF, Konijnenberg M, Bakker WH, Teunissen JJ, de Jong M, van Lom K, de Herder WW, Kwekkeboom DJ. Bone marrow dosimetry in peptide receptor radionuclide therapy with [177Lu-DOTA(0),Tyr(3)]octreotate. *Eur J Nucl Med Mol Imaging*. 2009;36:1138-1146.
- Pauwels S, Barone R, Walrand S, Borson-Chazot F, Valkema R, Kvols LK, et al. Practical dosimetry of peptide receptor radionuclide therapy with (90)Y-labeled somatostatin analogs. *J Nucl Med* 2005;46(Suppl 1):92S-98S.
- Sgouros G. Dosimetry of internal emitters. *J Nucl Med* 2005;46(Suppl 1):18S-27S.