PHYSICS ASPECTS OF THERAPEUTIC NUCLEAR MEDICINE

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Radiopharmaceuticals have been used to treat cancer for over 70 years. Molecular radiotherapy (MRT) is currently a major growth area with an increasing number of compounds entering the clinic and a rapidly expanding interest in the scientific aspects of radiation delivery. Whilst radiopharmaceuticals have generally been administered according to similar protocols defined for non-radioactive drug delivery, primarily with fixed activities or sometimes based on patient weight or body surface area, recent scientific advances in quantitative imaging and internal dosimetry are now causing a shift toward administrations that take into account individual dosimetry, as is routinely the case for external beam radiotherapy (EBRT). The relative lack of progress in MRT belies the fact that this area does not require the significant resources that are required for EBRT.

At a basic level, dosimetry can be considered separately for the whole-body, which requires external measurements of the activity retained in the patient following administration, or tumour or normal organ dosimetry, for which absorbed dose calculations are based on image data.

Whole-body dosimetry can be performed with relative ease and accuracy. An external measurement obtained immediately following administration of a radiopharmaceutical provides a baseline count relating to activity *in vivo*. Subsequent measurements can then be related to this baseline to provide an accurate calculation of the activity retained at any time. This is useful for radiation protection purposes but can also be used to calculate whole-body absorbed doses which have been shown to correlate with haematological toxicity. This is the basis for treatment with I-131 tositumomab for non-Hodgkins lymphoma, where patients are prescribed an activity that will deliver a 0.75 Gy whole-body absorbed dose and for an international study using I-131 mIBG to treat neuroblastoma, where the protocol is designed to deliver a total of 4 Gy whole-body absorbed dose in 2 fractions. The I-131 mIBG is given concomitantly with topotecan which is a topoisomerase inhibitor that can act as a radiosensitiser, indicating the potential for multi-modality therapy that is currently being explored. The accuracy of whole-body dosimetry can be calculated and is dependent in turn on the accuracy of measurements, which for example should be obtained immediately after patient voiding, and on the number of measurements acquired for each effective decay phase.

Image-based tumour or normal organ dosimetry can offer more detailed information regarding the localisation of uptake and retention of an administered radiopharmaceutical. Time-sequential images are acquired following administration and by application of suitable calibration factors activity-time curves are used to estimate the cumulated activities in user-defined regions of interest. Image-based dosimetry is prone to large errors and uncertainties if not performed correctly although can yield clinically useful information. It is essential that routine quality control (for example to correct for uniformity and centre-of-rotation misalignment) is performed to ensure that the camera is operating correctly and initial measurements should include characterisation of deadtime, as the large activities encountered

in MRT can cause erratic response. For the quantitative imaging required for absorbed dose calculations image corrections are essential although can be performed with relative ease. Scatter correction is particularly relevant for high energy beta emitters such as I-131 and can be performed by acquiring counts in energy windows adjacent to the peak window. For SPECT imaging, attenuation correction should be performed using measured attenuation coefficients for the radionuclide used. The optimal SPECT image reconstruction method or parameters to use for any given radionuclide have not been defined. These must be considered carefully and are dependent on the localisation of activity and count rate.

As with whole-body dosimetry, the accuracy of dosimetry calculations is dependent on the number of measurements (i.e. scans) obtained although in practice a total of 3-4 scans are usually sufficient as the effective decay in any given organ, or tumour, is frequently mono-exponential.

An increasing number of studies are now demonstrating that the effect of treatment, both in terms of response and toxicity, is dependent on the absorbed doses delivered to target and to normal tissues. This raises the prospect of personalised treatment planning, whereby the level and frequency of administrations are tailored to the individual patient. Patient-specific treatments promise a significant increase in the effectiveness of molecular radiotherapy and offer a significant improvement on current population-based treatments.

As only a small number of patients are treated at individual centres it is essential that prospective data collection is performed in multi-centre studies. However the variation in methods employed at different centres to perform dosimetry hinder direct comparisons of absorbed dose calculations. To address this, the EANM dosimetry committee are undertaking a program (DOSITEST) to assess the current range of methodologies employed and their relative accuracies to harmonise practice. This will involve an exercise whereby simulated raw camera data are supplied to centres that can then perform calculations according to local protocols.

Internal dosimetry has been shown to have clinical benefit and is becoming standard practice as requirements for personalised treatment are introduced and regulations regarding treatment planning are brought into force. The resources required to perform dosimetry are within reach of any department that has scanning facilities and can provide significant cost-effective patient benefit both by ensuring that sufficiently high absorbed doses are given to effect a favourable response and sometimes by preventing unnecessary treatments.