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COMMENTARY

Molecular radiotherapy — the radionuclide raffle?

[1]M N GAZE, MD and [2]G D FLUX, PhD

[1]*Department of Oncology, University College London Hospitals NHS Foundation Trust, London, UK, and* [2]*Joint Department of Physics, The Royal Marsden NHS Foundation Trust and Institute of Cancer Research, Sutton, Surrey UK*

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The medicinal use of unsealed radioactive sources for the treatment of cancer and other conditions has been undertaken clinically for over 50 years. The use of these sources has been known by a variety of names including isotope treatment, unsealed source therapy, (biologically) targeted radionuclide therapy and, most recently, molecular radiotherapy. The term ''molecular radiotherapy'' (MRT) will be used throughout this report to emphasise that treatment is based on the delivery of radiation to malignant tissue through the interaction of an agent with molecular sites and receptors.

Despite its history and undoubted place in the management of some cancers, and in spite of the extensive high-quality physics research that underlies its use, MRT has been a neglected, almost orphan, area of medical practice for several reasons.

Firstly, and paradoxically, the empirical success of radioactive iodine in the treatment of thyroid cancer has contributed to the lack of its scientific appraisal and to a lack of interest in the systematic evaluation of MRT in the management of other cancers. The cure of an epithelial cancer with minimal toxicity, even in the presence of lymphatic and blood-borne metastases, is remarkable. This is true even today, when more cancers are curable at the expense of significant treatment-related toxicity: half a century ago it was miraculous. This was seen as an expected, not exceptional, outcome from the earliest days of radioactive iodine treatment and has meant that there has been very little research into finding the optimal use of this treatment.

Secondly, physicians in more than one medical specialty have taken responsibility for the clinical management of patients who might benefit from some form of MRT. Both nuclear medicine physicians and clinical oncologists are closely involved in this area of practice, yet for very few is it the predominant clinical, or research, interest. In nuclear medicine, diagnostic investigations and the development of innovative techniques such as positron emission tomography (PET) imaging take precedence. Clinical oncologists are skilled in all aspects of the non-surgical management of patients with cancer, but their practice and research interests are usually focused on chemotherapy and external beam radiotherapy.

In specific areas, other medical specialists might quite reasonably lay claim to one area of MRT practice; for example, endocrinologists in the management of thyroid cancer and benign thyroid disease, haematologists in the management of leukaemia and lymphoma or paediatric oncologists in the management of neuroblastoma. Although experts in their own field, such individuals do not normally have experience of the wider applications of MRT or have a detailed understanding of the radiation physics and biology that form the scientific basis of this treatment. Therefore, these specialists are not well placed to develop the scientific understanding of this field further.

Thirdly, the scientific development and clinical evaluation of innovative MRT procedures is incredibly complex. New radionuclides with potential for improving therapies have become available. Research in molecular biology and immunology has uncovered new targets and developed new vectors. However, there are no dedicated academic departments, integrated with the required hospital facilities, for MRT development. These departments would need to bring together expertise in the preclinical and clinical aspects of radiobiology, radiochemistry, radiopharmacy, radiation physics and dosimetry. Oncology and clinical trials would also need to be linked seamlessly with these areas of expertise to take forward a programme of new ideas from the laboratory to the patients in the wide spectrum of diseases for which MRT might be beneficial. To a large extent, industry has had little interest in investing in this arena, as the perceived markets, even for an ultimately successful treatment, are too small in comparison with the cost of developing and evaluating a new treatment to the point of licensing. Although individual projects have been funded, cancer research charities have by and large not seen this as a priority area for investment.

Address correspondence to: Dr Glenn Flux, Joint Department of Physics, Royal Marsden Hospital, Downs Road, Sutton, Surrey SM2 5PT, UK. E-mail: glenn.flux@icr.ac.uk

Finally, no individual or organisation has taken up the challenge, nationally or internationally, of championing this treatment modality in all its aspects. Instead, many different committees (Nuclear Medicine and Molecular Imaging, Oncology, Radiation and Cancer Biology, Radiation Physics and Dosimetry and Radiation Protection), have some responsibility for where their area of interest might relate to unsealed source therapy. Bodies with responsibility for guiding cancer care such as the National Institute for Health and Clinical Excellence (NICE) and the National Cancer Research Institute (NCRI) have so far taken little interest in this treatment modality, although the NCRI Clinical and Translational Radiotherapy Research Working Group (CTRad) initiative actively acknowledged this area.

Here we report on the recent Molecular Radiotherapy Meeting, held at the British Institute of Radiology (BIR) on 6 February 2009. The meeting was organised by the MRT Working Party subgroup of the Radiation Physics and Dosimetry Committee of the BIR. Some of the data presented came from a national survey of current practice in MRT organised by the Working Party in 2008.

The main aim of this meeting was to raise the profile of MRT by bringing together interested individuals from all relevant professions and disciplines. By reviewing the clinical areas where MRT had achieved successful outcomes, and the pathways for investigating new clinical outcomes, it was hoped that new co-operative endeavours could be generated. The secondary aim was for the discussion and debate to inform the recommendations of a report on the current status of, and future prospects, for MRT in the UK being prepared by the Working Party for a forthcoming publication.

Presentations

Survey results

Dr Mark Gaze, Consultant Clinical Oncologist from University College London Hospitals NHS Foundation Trust, opened the meeting with a series of questions about MRT: What is it? What do we use it for? How do we use it now? What is needed to use it? How can we use it better? Who should use it?

It was hoped that some data from the 2008 survey of current practice, together with information from the other presentations, would allow these questions to be answered by the end of the day.

Thyroid cancer

Dr Masud Haq, Consultant Endocrinologist from the Maidstone and Tunbridge Wells NHS Trust, gave a presentation entitled *Thyroid cancer — questioning convention*.

He reviewed the role of radioactive iodine in the management of thyroid cancer and compared and contrasted the various recommendations given in three ''authoritative'' sets of guidelines regarding administered activities and the role of dosimetry. Although there is known to be a wide variation in the absorbed dose to the thyroid remnant following the administration of a fixed activity of radioactive iodine, and there is evidence that the success of thyroid remnant ablation is dependent on the absorbed dose received by residual thyroid tissue, the administration of a fixed activity without dosimetry is still the usual recommendation. Having said that, the recommended activity to be administered varies and there is a current trial comparing the effect of administering 1.1 GBq with 3.0 GBq.

Haematological malignancy

Professor Tim Illidge, Professor of Targeted Therapy and Oncology at the Christie NHS Foundation Trust, gave a presentation entitled *Haematological cancer — current approaches and challenges*.

Leukaemia and lymphomas are well suited to treatment by MRT because they are radiosensitive cancers expressing cell-surface antigens such as CD20. Antibodies directed against CD20 have an immunological cytotoxic effect that is synergistic with the radiation-induced cell death brought about by radiolabelling the antibody with ^{131}I or ^{90}Y. Clinical trials have shown excellent outcomes. For example, ^{131}I-tositumomab produces durable complete remissions in heavily pre-treated patients with low-grade and transformed non-Hodgkin's lymphomas and ^{90}Y-ibritumomab consolidation improves response quality in the majority of patients with conversion from partial to complete response, resulting in improved progression-free survival compared with no further treatment. However, the use of MRT has been limited by a lack of commitment from the pharmaceutical industry, the small number of centres with the necessary facilities and interested staff, the absence of recognition by NICE and the absence of defined funding streams.

Neuro-endocrine cancers

Dr John Buscombe, Consultant Nuclear Medicine Physician from the Royal Free Hampstead NHS Trust, gave a presentation entitled *Neuro-endocrine tumours — to dose or not to dose, that is the question?*

Metastatic neuro-endocrine tumours (NETs) are ideally suited to MRT as they express a number of molecular targets including the noradrenaline transporter and somatostatin receptors, which can be targeted with ^{131}I-meta-iodobenzylguanidine (^{131}I-mIBG), and labelled somatostatin analogues such as ^{90}Y-DOTA-octreotide and ^{177}Lu-DOTA-octreotate, respectively. In addition, liver metastases can be targeted by intra-arterial injections of ^{131}I-lipiodol or ^{90}Y-sirspheres. Reported results can vary widely because of the heterogeneity of patients treated, the end point measured (*i.e.* symptomatic response, reduction of tumour markers, nuclear scan improvement or radiological criteria such as RECIST (Response Evaluation Criteria in Solid Tumors)) and the timing of the assessment. For these reasons it is difficult to compare the effectiveness of different radionuclide/vector combinations without a randomised trial. Dosimetry of tumour and dose-limiting normal tissues (*e.g.* kidney and marrow) might be estimated from pre-therapy PET studies or performed following therapy administration. Dosimetry is rarely used as initial studies have shown no correlation between the tumour absorbed dose and response.

Paediatric malignancy

Dr Naomi Fersht, Locum Consultant Clinical Oncologist from University College London Hospitals NHS

Foundation Trust, gave a presentation entitled *Childhood cancer — ensuring there is a future*.

The principal indications for MRT in childhood and adolescence are neuroblastoma (^{131}I-mIBG) and thyroid cancer (Na^{131}I). The main challenges in this age group are logistic. Specialised facilities in an age-appropriate environment with experienced paediatric nurses and doctors and supportive care staff such as play specialists are required. Children in hospital need care and comfort and no one is better placed to give this than appropriately trained, informed and consenting parents. The inevitable radiation exposure can be reduced to acceptable amounts by minimising contact time, consistent with delivering the care required, maximising distance and introducing protective barriers.

Introduction of new agents

Professor Steve Mather, from Barts and the London School of Medicine and Dentistry, asked the question: How do you take a potential therapeutic radiopharmaceutical into clinical trials in an academic setting?

The answer it seems is long and complex. Firstly, an extensive pre-clinical programme is required to evaluate the chemistry and stability of the radiopharmaceutical preparation and its efficacy against the target both *in vitro* and in xenograft models. A series of Phase I, II and III clinical trials are then required to evaluate toxicity and efficacy in patients. The regulatory environment includes sponsorship, ethical opinions, Medicines and Healthcare products Regulatory Agency (MHRA) licensing, Administration of Radioactive Substances Advisory Committee (ARSAC) approval and local Research and Development approval. Various codes of practice govern different stages: the product must be prepared according to Good Manufacturing Practice (GMP), assays performed to Good Laboratory Practice (GLP) and trials constructed according to Good Clinical Practice (GCP). All this, of course, is dependent on funding. Although cancer research charities make grants available for good projects, these usually cover running expenses only and are conditional on the appropriate infrastructure being in place.

Internal dosimetry

Dr Matt Guy, Nuclear Medicine Physicist at the Royal Surrey County Hospital in Guildford, gave a presentation entitled *The current status and future directions of internal dosimetry for molecular radiotherapy.*

Internal dosimetry has been used sporadically in previous decades, mainly on an *ad hoc* basis and with little consistency regarding the methods used. Despite the few studies performed, there is increasing evidence that the effect of treatment corresponds to the absorbed doses delivered to tumours and to normal organs rather than to the administered activities. Particular benefit can be obtained from dosimetry for thyroid cancer, neuroendocrine tumours and intra-arterial treatment for liver cancer. Scientifically and clinically valid results can only be obtained from accurate dosimetry, which requires careful attention to data acquisition and processing. Internal dosimetry is essential to the future development of MRT.

Resources

Dr Kim Orchard, Consultant Haematologist from Southampton, gave detailed consideration to *Resources – the centre requirements to provide a good service for molecular radiotherapy.*

Taking full account of patient and environmental safety, clinical outcomes and patient experience, the delivery of MRT is a complex multiprofessional and multidisciplinary endeavour. Many staff, appropriately trained to the required levels of knowledge and competence, need to work together with excellent communication and a defined governance structure. Different types of unsealed source treatment require different levels of infrastructure. These range from Level 1, outpatient treatment with no dosimetry, to Level 3 for specialised services involving novel radiopharmaceuticals or the application of standard radiopharmaceuticals in new indications. This infrastructure requires, among other things, a specialist radiopharmacy, dedicated inpatient facilities with radiation protection, protected accommodation for relatives, methods for safe storage of radioactive waste (including sewage and waste with low-level contamination) and nuclear medicine imaging for tumour and normal organ dosimetry.

A new medical subspecialty devoted to the development and practice of MRT?

The meeting concluded with a lively debate: ''This house believes that targeted radionuclide therapy should be recognised as an independent medical specialty''. The debate was chaired by Dr Val Lewington (Consultant Physician of the Royal Marsden NHS Foundation Trust in Sutton). Dr Glenn Flux led the arguments for the debate, whilst Dr Mark Gaze considered those against. It is clear that a wide range of knowledge and skills are required and that a multidisciplinary team effort is necessary to deliver a comprehensive service. Conventional training for oncologists and nuclear medicine physicians fails to deliver all of these. In general, it was agreed that a further medical specialty would further muddy the waters, but that some form of subspecialist credentialling for members of all disciplines who wish to develop expertise and a specialist practice in this area might be advantageous. Other aspects of MRT delivery were also considered, such as the extent to which patients would be prepared to travel to ''centres of excellence'' should they exist.

Conclusion

This fully attended meeting provided a well-balanced view of the current state of MRT in the UK and gave ample opportunity for those interested in this field to express their views. It was evident that despite, or perhaps because of, the multidisciplinary nature of this treatment, all scientists and physicians were enthusiastic about this topic and that it would continue to expand.

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