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Clinical Trials and Molecular Radiotherapy

This issue of "WJNM" is heavily biased in favor of the use of radionuclides in molecular radiotherapy. This is of course appropriate, as the journal has strong links with the World Association for Radionuclide Molecular Therapy (WARMTH). We, the editorial team, are very proud that many authors from institutions around the globe choose this journal to publish their results and share possibilities for treating patients with a range of benign and malignant conditions. Newer radionuclides such as Re-188 and Lu-177 are being coupled to new pharmaceuticals, and these enable an increasing range of therapies to be developed. However, there remains a real issue. In the hands of enthusiastic nuclear medicine physicians, many patients receive effective treatments targeted to their particular clinical problem with minimal toxicity, functioning as truly personalized medicine, but worldwide this only applies to a minority of patients suffering from any particular disease. The use of molecular radiotherapy is still not universal. For many molecular radiotherapy techniques, the chance of a patient having access to a particular treatment may be down to nothing more than luck. They are fortunate if they are born in a particular country or even a particular city and are looked after by a doctor who has knowledge of molecular radiotherapy techniques, who is willing to refer to a nuclear medicine physician trained to administer that treatment. Surprisingly, it is not just a matter of money. In many cases, a patient living in one of the world's richest economies such as the USA or Japan may have as much chance of referral as a patient living in Togo or Bhutan.

So why can we not convince our colleagues of the utility of our techniques? A long-term criticism of the nuclear medicine world has been that it does not perform multicentre, randomized clinical trials (RCTs). Such RCTs are the currency of oncology, and, to some extent, oncology developed as a specialty not to treat patients with cancer but to perform RCTs, often for a commercial company. In his book *Sympathy for the Devil*, Dr. Gary Acton gives many examples of RCTs and in particular their high failure rate, which not only ends the possibility of a particular drug entering the market but can result in the collapse of whole companies.[1]

So what has this to do with molecular radiotherapy, because we know our techniques are successful—or do we? It is easy to fool ourselves. Both we and our patients are susceptible to the placebo effect and may wish that any treatments we give are successful, but do we really know that they are? All new pharmaceuticals need to pass through three phases of clinical trials. In the first phase, normally 10-20 patients are studied in a dose-escalation study. A series of dose escalations are included with normally three patients per step until significant toxicity occurs in one or more of the patients in that phase. The toxicity of this dose would have to be enough for the patient to need hospital admission. The dose before it is then picked as the maximum tolerated dose. This can be difficult in molecular radiotherapy, as the maximum administered activity we give may be restricted by other factors including the legal limits of radioactivity that can be used, radiation dose to staff, and costs. However, it is possible to design and perform a good dose-ranging study to determine the maximum tolerated dose.[2]

The second phase is one at which nuclear medicine tends to be good and it is called a phase 2 or proof-of-concept study. For a patient with cancer, a phase 2 study would be performed if their cancer was fairly advanced and likely to kill them (though not too soon), and if more conventional treatments have failed. The general wisdom is that only 150-200 patients need be treated, though some phase 2 trials have more patients.[3] To reduce bias, these studies should take place in more than one center, with similar patients studied and the same treatment given. Response should be measured by previously agreed-on criteria. Many forms of radionuclide therapies do not advance beyond this phase and are therefore not funded by governments or insurance providers.

Those who pay for a treatment like to know how it compares to standard treatment techniques before they reimburse the therapy. In an RCT, a group of patients with similar conditions are randomly assigned to two groups; one receives the new treatment while the other receives nothing, a placebo, or standard care. This study should take place in different hospitals, ideally in different countries and different types of hospital such as regional, national, and specialist cancer centers. If possible, neither the patient nor the clinician knows

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whether the patient has received treatment. This may mean that posttherapy imaging may not be possible. The number of patients to be studied should be no less and no more than will show that the treatment has a significant effect compared to the untreated arm. This must be monitored by those not involved in the trial and may mean that the numbers treated could be as high a 1000 patients per study.[4] This is not a process that can be undertaken cheaply or without significant commitment, but it is possible for academic organizations and networks to achieve.[5] I know we are asking a lot but if we really believe that our patients will benefit from the techniques we use, we owe it to them to set up and run these trials in the same way that groups of oncologists have done.

In 1980, the number of specialist oncologists in the world was about 10% the number of nuclear medicine physicians; now they outnumber us by a factor of 10. Why? Because they embraced evidence-based medicine and the RCT. We, too, as nuclear medicine physicians need to be so organized, either through specialist organizations or through cooperative groups such as the European Union Horizon 2020 initiative. As we go forward in this great endeavor, I encourage all of us to learn to work together for the common good of our patients.

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References

1. Acton G. Sympathy for the devil. London: Matdor; 2013.
2. Dancey G, Violet J, Malaroda A, Green AJ, Sharma SK, Francis R, *et al*. A phase I clinical trial of CHT-25 a 131I-Labeled chimeric Anti-CD25 antibody showing efficacy in patients with refractory lymphoma. Clin Cancer Res 2009;15:7701-10.
3. Kwekkeboom DJ, de Herder WW, Kam BL, van Eijck CH, van Essen M, Kooij PP, *et al*. Treatment with the radiolabeled somatostatin analog [177 Lu-DOTA 0, Tyr3] octreotate: Toxicity, efficacy, and survival. J Clin Oncol 2008;26:2124-30.
4. Sartor O, Coleman R, Nilsson S, Heinrich D, Helle SI, O'Sullivan JM, *et al*. Effect of radium-223 dichloride on symptomatic skeletal events in patients with castration-resistant prostate cancer and bone metastases: Results from a phase 3, double-blind, randomised trial. Lancet Oncol 2014;15:738-46.
5. Mallick U, Harmer C, Yap B, Wadsley J, Clarke S, Moss L, *et al*. Ablation with low-dose radioiodine and thyrotropin alfa in thyroid cancer. N Engl J Med 2012;366:1674-85.

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