Targeted Radionuclide Therapy: Practical Applications and Future Prospects

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Supplementary Issue: Biomarkers and their Essential Role in the Development of Personalised Therapies (A)

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ABSTRACT: In recent years, there has been a proliferation in the development of targeted radionuclide cancer therapy. It is now possible to use baseline clinical and imaging assessments to determine the most effective therapy and to tailor this therapy during the course of treatment based on radiation dosimetry and tumor response. Although this personalized approach to medicine has the advantage of maximizing therapeutic effect while limiting toxicity, it can be challenging to implement and expensive. Further, in order to use targeted radionuclide therapy effectively, there is a need for multidisciplinary awareness, education, and collaboration across the scientific, industrial, and medical communities. Even more important, there is a growing understanding that combining radiopharmaceuticals with conventional treatment such as chemotherapy and external beam radiotherapy may limit patient morbidity while improving survival. Developments in radiopharmaceuticals as biomarkers capable of predicting therapeutic response and targeting disease are playing a central role in medical research. Adoption of a practical approach to manufacturing and delivering radiopharmaceuticals, assessing patient eligibility, optimizing post-therapy follow-up, and addressing reimbursement issues will be essential for their success.

KEYWORDS: targeted, radionuclide therapy, oncology

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Introduction

Targeted radionuclide therapy (TRT), the use of one or more radionuclides for targeted therapy at the cellular or molecular level, has been around for many years. The first application in oncology was in the 1940s when physicians began imaging and treating patients with thyroid disease using radioactive iodine.[1] Radioimmunotherapy (RIT), the use of a radiolabeled monoclonal antibody for targeted therapy, is more recent than TRT, although this is also more than 30 years old.[2] In 2002, ^{90}Y-ibritumomab tiuxetan (Zevalin; Spectrum Pharmaceuticals, Inc.), a radiolabeled anti-CD20 monoclonal antibody, was the first RIT to receive Food and Drug Administration approval for the treatment of patients with relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin lymphoma (NHL).[3] This was followed in 2003 by ^{131}I-tositumomab (Bexxar; GlaxoSmithKline, Inc.), which is also a radiolabeled anti-CD20 monoclonal antibody for the treatment of patients with NHL.[4] Radioactive iodine therapy, Zevalin, and Bexxar have been, arguably, the most commonly used TRT and RITs throughout the history of clinical nuclear medicine.

Recently, interest in the medical community for TRT and RIT has been growing. The mechanism of cell death following TRT exposure can result both from a direct radiation effect and from crossfire and bystander effects.[5] There are several commonly used targeted radionuclide therapeutic agents (such as ^{131}I and ^{90}Y), and the choice of radionuclide depends on the tumor characteristics. For example, radionuclides that emit high-energy alpha or beta particles are preferred for the treatment of bulky tumors, although radionuclides that emit Auger electrons are considered to be beneficial for the eradication of small clusters of cancer cells or small tumors. Most radionuclides are metals, and care must be taken to choose an appropriate chelating agent tailored to the TRT application and radionuclide being used.[6] The mechanism of cell death following RIT is two pronged: (1) apoptosis due to radiation exposure and (2) the effect of the host immune response against target cells, including induction of apoptosis through

direct signal transduction, complement-mediated cytotoxicity, and antibody-mediated cellular cytotoxicity.[7]

One of the most appealing benefits of TRT and RIT is the possibility for personalized medical care, optimized for patient and disease characteristics. Unlike conventional systemic chemotherapy, TRT and RIT allow radiation to be delivered directly to the targeted site of disease with potentially less toxicity from exposure of normal tissues. There are several considerations that must be kept in mind while designing a personalized treatment plan for patients. Namely, treatment decisions should be informed using a combination of clinical findings and biomarkers/imaging to assess baseline disease extent, likelihood of response to a given radiopharmaceutical, and to calculate the optimal amount of radioactivity needed for maximal therapy with minimal or manageable toxicity. In order to choose the appropriate TRT or RIT and estimate the amount of radioactivity to be given, pretherapy treatment planning may be needed. This would likely require additional patient visits, imaging, and potentially interventional procedures, which can be challenging both for the treating physician and for the patient to arrange and perform.[8]

In 2013 and 2014, the Society of Nuclear Medicine and Molecular Imaging and the National Cancer Institute partnered to host two joint workshops on TRT, bringing together members from the scientific, clinical, and industrial communities to review what had been learned about TRT and to explore the approach needed to bring advances into medical practice.[6,9] The current increase in baseline imaging to identify disease sites, predict response to therapy, and determine the specific treatment needed to achieve optimal results was discussed. The advantage of evaluating the effect of therapy both clinically and with imaging and then using these results to modify treatment for maximal patient benefit was reviewed. It was agreed that for TRT to be widely adopted, several challenges would have to be overcome and close collaboration between members of the medical team, the scientific community, and industry would be key.[6,9]

Current Applications

Today, TRT and RIT are encountered daily in many nuclear medicine clinics, typically for the treatment of patients with thyroid cancer, metastatic prostate cancer, and lymphoma.

Thyroid cancer is the most common endocrine malignancy with an estimated 62,450 new cases and 1,950 deaths in 2015.[10] Radioactive iodine therapy is commonly used for the treatment of well-differentiated thyroid cancer. Although generally well tolerated, there are both short- and long-term complications of using radioiodine treatment. Early complications may include thyroiditis, gastrointestinal symptoms, sialadenitis/xerostomia, dry eyes, and bone marrow suppression while late complications may include pulmonary fibrosis, secondary cancers, and permanent bone marrow suppression among others.[11] In recent years, the indications, efficacy, and amount of activity given have been debated. Advocates for a personalized approach to TRT in patients with thyroid cancer promote the need for selective administration of radioactive iodine and use of lower amounts of radioactivity to minimize toxicity whenever possible.[12] According to the American Thyroid Association, thyroid cancer patients are classified as low risk when there is no macroscopic disease following surgery, no metastases, vascular invasion, or aggressive histology. Intermediate-risk patients may have microscopic tumor invasion into the soft tissue adjacent to the thyroid gland, lymph node spread, vascular invasion, or radioactive iodine uptake outside the thyroid gland on a radioactive iodine scan. High-risk patients have macroscopic tumor invasion, distant metastases, and potentially high thyroglobulin levels out of proportion with the postradioactive iodine therapy scan. Although adjuvant radioactive iodine therapy is not recommended for low-risk patients, it is recommended for high-risk and for most intermediate-risk patients.[13] Indeed, a recent review of over 21,000 patients treated for intermediate-risk papillary thyroid cancer showed that the addition of adjuvant radioactive iodine therapy resulted in a reduction in the risk of death by approximately 30%.[14] High-dose radioiodine therapy is also helpful for advanced disease at presentation, local recurrence that is not amenable to surgery alone, and distant metastatic disease.[15]

Prostate cancer is the most commonly diagnosed malignancy in men with an estimated 220,800 new cases and 27,540 deaths in 2015.[16] TRT has been used for the palliation of bone pain from metastatic prostate cancer for several years; however, radium-223 dichloride (Xofigo; Bayer Healthcare Pharmaceuticals) was the first approved alpha-emitting radiopharmaceutical and the first TRT shown to extend life in men with castration-resistant disease.[17] In the last 3 years, Xofigo has become increasingly ubiquitous in routine oncologic clinical practice. Although shown to increase overall survival and delay the time to first skeletal related event, there are adverse reactions, including gastrointestinal symptoms, peripheral edema, and bone marrow suppression. Most complications are short-term with long-term complications such as bone marrow failure being uncommon.[18] The incidence of secondary malignancies is unknown.

Unlike TRT, RIT using antibodies or antibody fragments to target tumor cells is uncommonly encountered in the nuclear medicine clinic today. Rituximab is a chimeric IgG_1 anti-CD20 monoclonal antibody that is used in combination with chemotherapy in the treatment of patients with lymphoma. The idea of RIT stems from the belief that adding a radioisotope to an anti-CD20 monoclonal antibody would augment effectiveness by enabling targeted radiation therapy. In general, radioisotope conjugation is thought to improve efficacy, although patients have shown impressive responses using the nonradiolabeled antibody as well. Zevalin (ibritumomab tiuxetan) is a monoclonal mouse IgG_1 anti-CD20 antibody in conjunction with the chelator tiuxetan, to which a radioactive isotope (^{90}Y) is added for the purposes of targeted

radiation therapy. It is the most commonly used RIT and has been available for over 15 years for the treatment of relapsed or refractory low-grade follicular lymphoma or transformed B-cell NHL, including rituximab-refractory follicular NHL. Zevalin can improve progression-free survival and is associated with improved overall response rate in advanced follicular lymphoma compared with using rituximab alone.[19–21] In addition, Zevalin has the advantage that a one-time administration is needed compared with multiple cycles of chemotherapy. It is thought that the limited use of Zevalin has been, at least in part, due to lack of expertise and collaboration between oncologists and nuclear medicine physicians, poor patient access, concerns about radiation safety, and issues related to reimbursement.[6,9] Bexxar (tositumomab) is a monoclonal mouse IgG_{2a} anti-CD20 antibody to which a radioactive isotope (^{131}I) is added for the purposes of targeted radiation therapy. Although treatment of similar patient groups with either Zevalin or Bexxar has yielded comparable results, there are no head-to-head comparisons of efficacy in randomized trials. Bexxar is less commonly used than Zevalin, possibly due to the fact that multiple visits are needed to determine the administered activity to maximize tumor response while minimizing toxicity. In addition, since the radioisotope label is ^{131}I, this can result in thyroid exposure necessitating premedication. The most important serious adverse effect of both Zevalin and Bexxar is severe prolonged cytopenia. Recently, there has been interest in designing randomized trials capable of defining the role of RIT within the cadre of available treatment, resolving reimbursement issues and improving access, at least in part through increased personnel training and collaboration.[6,9] Today, RIT is typically integrated into the treatment of patients with relapsed or refractory follicular lymphoma or as consolidation after induction chemotherapy. RIT may also have a place in first-line or follow-up therapy for patients with B-cell NHL and in other hemopathies such as multiple myeloma.[22]

Future Prospects

There is a growing availability of novel TRT for the treatment of patients with cancer. One of the areas of active research involving TRT is the treatment of neuroendocrine disease. Neuroendocrine tumors constitute a heterogeneous group of diseases with limited treatment options. Peptide receptor radionuclide therapy (PRRT) is a targeted therapy that uses peptides radiolabeled with either ^{90}Y or ^{177}Lu to deliver radiation to cancer cells that express somatostatin receptors. There has been considerable interest in PRRT because of the advantages inherent to targeted therapy at the molecular level that allows for minimal toxicity to nontargeted tissue. Indeed, PRRT has been shown to be well tolerated and can improve symptomatic control, progression-free survival, and overall survival for patients with metastatic and/or progressive neuroendocrine malignancy.[23,24] The principal short- and long-term adverse effects are renal and hematologic toxicity (myelodysplastic syndrome and acute leukemia), and there is ongoing work to establish strategies for minimizing this. Although not yet routinely available in North America, the experience in Europe dates from 1994 when PRRT was first used in Krenning's group in Rotterdam. Indeed, the European Neuroendocrine Tumor Society Center of Excellence at Zentralklinik Bad Berka has more than 1,200 patient visits and administers more than 500 cycles of PRRT every year.[6] Research is also underway to establish the optimal combination of TRT using ^{90}Y- and/or ^{177}Lu-labeled radiopharmaceuticals[25] and nonradionuclide based therapy such as chemotherapy.[26]

It is also becoming increasingly possible to image sites of disease and then target these sites of disease using radionuclide therapy. Over the last 10 years, there has been a proliferation of metabolic imaging agents and a host of new therapies for men with prostate cancer. TRT with Xofigo is becoming standard of care therapy for men with metastatic prostate cancer and research, regarding the role of Xofigo within the armamentarium of available prostate cancer therapy is ongoing. Several imaging studies have evaluated PET/CT for the detection of prostate cancer using agents that target fatty acid metabolism such as ^{11}C-choline, ^{18}F-choline, and ^{11}C-acetate[27–29] or amino acid transport such as anti-^{18}F-FACBC.[30] Recent literature has suggested that radiotracers target the prostate-specific membrane antigen (PSMA) that could be used pre-therapy as a biomarker for differentiating aggressive from indolent disease.[31] Radiopharmaceuticals targeting PSMA could also provide the possibility of combining imaging and TRT in this patient population.[32]

There is ongoing research in the development of novel TRT and RIT, the approach for calculating the optimal amount of radiotracer to be administered, the possibility of developing new methods of radionuclide delivery, and the role of combination therapy.[7,33] Indeed, TRT and RIT may be synergistic in combination with existing medical therapy and could augment the effectiveness of external beam radiotherapy by increasing radiation dose to both macroscopic tumor and micrometastases.[34] The benefit to patients would be more effective cancer treatment with reduced toxicity. It is also anticipated that there will be much research and development activity in therapy-diagnostic pair radiopharmaceuticals (theragnostics) for a variety of cancers. Cancer is a heterogeneous family of disease and to develop a personalized approach to therapy, unbiased, accurate information will be needed on the role of radiopharmaceuticals within the spectrum of available therapy. In addition, the criteria necessary to chose the most appropriate patient and disease-specific targeted oncologic therapy will need to be defined likely using biomarker/imaging information for patient stratification similarly to what has been done in other fields.[35,36] Finally, research providing robust data on patient outcomes including quality of life and impact on overall survival must be actively pursued.

Conclusion

As our understanding of the molecular basis of disease continues to expand, TRT and RIT are becoming an area of significant interest and growth. There has long been an understanding of radionuclide chemistry and physical characteristics of radionuclides; however, this is now being coupled with tumor-specific targeting agents such that imaging biomarkers of disease can be combined with radionuclide therapy. Based on our past experience with RIT for lymphoma, there is a need to foster collaboration between members of the health care team to promote easy access to radionuclide therapy and education about the benefits and risks for physicians and patients. Adoption of a practical approach to manufacturing and delivering radiopharmaceuticals, assessing patient eligibility, ensuring posttherapy follow-up, and addressing reimbursement issues will be essential for success. There is so much that can be done with radionuclide therapy. The question that is likely to arise is not, can we do it but rather, where does it fit into our treatment strategy and how do we best implement it?

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Wrote the first draft of the manuscript: KZ and FF. Contributed to the writing of the manuscript: KZ, HJ, JC and FF. Agree with manuscript results and conclusions: KZ, HJ, JC and FF. Jointly developed the structure and arguments for the paper: KZ, HJ, JC and FF. Made critical revisions and approved final version: KZ, HJ, JC and FF. All authors reviewed and approved of the final manuscript.

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