Editorial

The World Association of Radiopharmaceutical and Molecular Therapy position statement on the initial radioiodine therapy for differentiated thyroid carcinoma

INTRODUCTION

The World Association of Radiopharmaceutical and Molecular Therapy (WARMTH) is a worldwide nonprofit organization, which is dedicated to educating medical professionals in the use of radionuclide therapies based on the theragnostic principles and to harmonizing appropriate evidence-based practices worldwide.

Radionuclide therapy with radioiodine for thyroid conditions has been utilized for over 77 years since the first use of radioiodine (RAI) in a patient by Saul Hertz.[1] Over the years, new radionuclides of iodine have been introduced, which have improved diagnostic imaging quality. However, the basic concept of using a radiopharmaceutical to interrogate its affinity for a molecular target, in this case the sodium–iodide symporter, and later use of a biosimilar or identical agent formulated to deliver a radiation-absorbed dose to achieve a therapeutic effect remains the most enduring example of an optimal theragnostic approach.[2] Radiotheragnostic approach takes advantage of using a targeted radiopharmaceutical that demonstrates avidity to the disease-affected organ(s) or cells in an orderly manner. First, the avidity of the theragnostic radiopharmaceutical to the target is tested by administration of a diagnostic activity of the agent or its biosimilar analog labeled with the same or a radioisotope with optimal imaging characteristics. Second, the therapeutic activity of the theragnostic radiopharmaceutical is selected based on the information obtained from the diagnostic radiopharmaceutical, as well as taking into consideration ancillary diagnostic factors, such as other diagnostic imaging modalities, laboratory markers of the disease process as well as relevant physical and functional patients' characteristics. Since the introduction of RAI, there have been many attempts to discover and develop another "magic bullet" for diagnosis and therapy using a variety of radiopharmaceuticals that only recently began to bear fruit in cancer management.[3]

There are many international guidelines addressing RAI therapy in the differentiated thyroid cancer (DTC), such as from the European Association of Nuclear Medicine (EANM),[4] the Society of Nuclear Medicine and Molecular Imaging,[5] the American Thyroid Association (ATA),[6] as well as many national guidelines. They all differ significantly in principles and recommendations, for example, European panelists suggested modifications to approximately one-third of ATA 2015 recommendations. Those varying perspectives stimulated continuing debates, and the stakeholders concede that additional research is needed to resolve discrepant recommendations and potentially improve patient outcomes.[7] The WARMTH is a key stakeholder organization that is inherently enabled to facilitate a worldwide outreach to all professionals authorized in safe and effective administration of RAI therapy. Hence, in this introductory position statement, the WARMTH will channel its collective understanding of the first or initial RAI (iRAI) administration post total or near-total thyroidectomy for DTC and goals for the future investigations. The statement is also aimed to facilitate understanding of the key issues and homogenize the appropriate use of terminology in the memberships' countries of practice. The WARMTH will also seek to issue further position statements on the various key matters, including, but not limited to the need for preablation scans, the need for single-photon emission computed tomography-computed tomography (SPECT-CT) in addition to whole-body (WB) scans, the role of thyroglobulin (Tg) measurement, the use of hormone withdrawal versus recombinant human thyroid-stimulating hormone (rhTSH) stimulation, the role of fluorine-18-fluorodeoxyglucose-positron emission tomography-CT (^{18}F-FDG-PET-CT), optimum treatment and follow-up regime, role of dosimetry, role of tyrosine kinase inhibitors, and when to discharge patients to community care.

RADIOACTIVE IODINE FOR DIFFERENTIATED THYROID CANCER

In patients with DTC, RAI WB and neck imaging can be used to evaluate residual postoperative benign thyroid remnant, detect residual disease in the postoperative bed and residual metastatic disease in the neck or distant sites, as well as identify recurrent disease following therapy.

The aims for RAI therapy include:[6,8]

1. Remnant ablation
2. Adjuvant treatment
3. Treatment of known disease.

The iRAI administration can be given to ablate residual benign thyroid tissue.[9] This enables Tg test to be used for the detection of a residual DTC and/or for detection of a later recurrence. The adjuvant therapy is aimed at treating microscopic thyroid cancer that is presumed to be iodine avid. Its presence is usually signaled by elevated Tg in excess of what would be anticipated as solely the product of the remnant benign tissue that can be quantified on RAI uptake and scan. When pathology reveals positive surgical margins, it is given that microscopic tumor is left in the remnant thyroid tissue. Finally, therapy of metastatic disease is indicated when pretherapy RAI scan identifies a metastatic site or sites for RAI therapy, which can be administered using either empirical or dosimetric approaches. The above-described breakdown is not always possible in clinical practice as a significant uncertainty may remain at the time of iRAI administration. In such instances, it is most appropriate to qualify the therapy generically, as the "iRAI administration," without committing to one of the three above-specified options.

In considering appropriateness for iRAI therapy, the EANM guidelines are viewed as more certain,[4] while the 2015 ATA guidelines critiqued as being more ambiguous, which can lead to variable interpretation and greater practice variability.[6] The UK national multidisciplinary guidelines[10] indicate that the majority of patients with a DTC > 1 cm in diameter would need iRAI after total or near-total thyroidectomy. Patients with DTC of 1 cm or less with the low-risk characteristics can be treated with hemithyroidectomy and without RAI therapy according to the same document. The tumors between 1 and 4 cm would be considered for RAI therapy individually, based on the multiple risk variables.[10] The WARMTH recognizes that tumor size and other clinic-pathologic characteristics are general indicators of risk status for DTC patients, but they are certainly rather simplistic and nonspecific. For example, each member of this writing panel treated primary DTC microcarcinoma with extensive metastases.[11] While histopathological features are more sophisticated than size alone for risk characterization, they also lack the kind of specificity that could reliably differentiate between those patients who will do well without total thyroidectomy and/or iRAI therapy from those who would not. The molecular and genomic markers hold the greatest promise for accurate determination of an individual DTC patient prognosis and for enabling theragnostic iRAI treatment in the manner most aligned with precision medicine. Progressive approaches are now combining molecular-genomic features with clinicopathologic characteristics to produce novel indices through sophisticated computer-modeling approaches,[12] which could soon make currently used systems that are based on the size and histopathology appear antiquated.

The WARMTH strongly supports guidelines that promulgate thyroidectomy performance by a qualified surgeon with a consistently high practice volume (20–25 thyroid surgeries per year or more),[10] and postoperative management at centers with an established thyroid cancer multidisciplinary team. However, the WARMTH acknowledges that this practice may not yet be available in some resource-constrained regions and countries. It is encouraged that such multidisciplinary thyroid cancer teams, as well as access to a second opinion by a thyroid cancer histopathology specialist,[13] are expeditiously developed worldwide.

Over the last decade, there has been a move toward a more dynamic risk-based approach to RAI therapy for DTC. Such risk stratification could be based on the multimodality information, including postthyroidectomy Tg measurements and appearances on neck ultrasonography, sometimes in lieu of using whole-body RAI imaging. There is a recent tendency to personalize iRAI therapy based on the limited and conflicting risk data obtained from observational studies.[14] However, when there are >16 different staging systems defining the risk, it proves difficult to have a homogeneous process to the selection of administered activity for the initial ^{131}I treatment.[14]

The conflict in administering higher activities that could increase chances of treating any potential microscopic metastases, as compared to lower activities, is that it may also increase the risk of subsequent malignant neoplasm (SMN) and salivary dysfunction, as well as (depending on local regulations) increase hospital costs and radiation protection of the staff. The two prospective trials, HiLo[15] and ESTIMABL1,[16] aimed to better understand differences in outcomes between administering lower and higher iRAI activity. There are also other prospective trials underway to evaluate clinical safety of omitting iRAI therapy under certain scenarios, for example, Iodine or Not (IoN) trial[17] and ESTIMABL 2, as there are no published prospective trials with sufficiently long follow-up that could provide reliable basis for deciding whether it is better to withhold or administer iRAI therapy and if so, what would be the best activity. In this disease, which may often recur 10 to (in rare cases) 30 years later, the current trials with 5–10 years of follow-up may be of limited value.

The primary end point of the two prospective studies – HiLo and ESTIMABL1 – was iRAI administration efficiency.[15,16] Success rates were similar for "low" (30 mCi/1.1 GBq) and "high" activity (100 mCi/3.7 GBq) of ^{131}I. A statistically insignificant but higher rate of success was found in the higher RAI activity-treated group (90.2%) as compared to the lower activity group (84.3%) (both under rhTSH stimulation),

supporting noninferiority of the lower activity.[15] These outcomes could suggest that in general, the volume of residual thyroid tissue is small resulting in a high-absorbed dose even with low-administered activities. The 5-year outcomes of ESTIMABL1 trial have only recently been reported with a disease-free survival of 98%.[18] However, the extent of disease or subsequent recurrences could not have been predicted by the risk stratification before iRAI therapy. In fact, it is uncertain from the information provided whether those patients would be recommended for iRAI therapy based on the 2015 ATA guidelines. At the same time, new evidence is growing in support of the RAI theragnostic approach to DTC,[19] which bears a more logical point of view.

There is a general agreement for using higher activities in patients with a high risk of recurrence.[4,6,10] The question, however, remains on whether lower activities or any treatment at all should be used in low-risk patients to reduce the frequency of SMN and other complications, as well as the length of hospital stay (a significant administrative hurdle in some countries with stricter regulations). There are conflicting reports with some suggesting increased risk of SMN, while others report on no change or even fewer malignancies after the RAI treatment.[20]

Furthermore, nonthyroidal primary tumors (particularly breast cancer and hematological malignancies) are relatively common in patients with DTC and usually antecede the DTC.[21] The individual variations in DNA repair efficiency after the radiation exposure are also a modifying factor to be borne in mind.[22]

PATIENTS' AND BROAD MEDICAL STAKEHOLDERS' INVOLVEMENT

^{131}I treatment has been the most enduring story of targeted radionuclide therapy and theragnostics. However, it is important to remember that with current access to information, patients are aware about risks of radiation exposure and, in particular, the possibility of SMN. A clear statement in layman terms that address the balance between benefits and the relative risks is required for providing the patient with actionable information. Informative studies on patient perceptions about and experience with radiotheragnostics are mostly lacking. The WARMTH will endeavor to develop the thyroid patients' forum to facilitate the exchange of their experiences with RAI treatments, their interactions with the health-care providers and sharing patients' life stories, as well as to allow for systematic surveying to provide feedback that could be invaluable in improving patients' future experience with RAI treatments. Patients' involvement should be a priority for the Nuclear Medicine Community. The WARMTH is also committed to multidisciplinary decision-making and will endeavor to actively encourage engagement with surgeons, oncologists, endocrinologists, pathologists, nuclear medicine physicians, radiologists and other key members involved in the management of thyroid cancer patients.

SUMMARY

The WARMTH has the benefit of being a worldwide organization with experts in the development and use of radionuclides and radiopharmaceuticals around the globe. The effectiveness of ^{131}I for treating DTC is well recognized. However, controversies on the optimal ^{131}I treatment activity and specific indications continue, while the risk stratification has not been harmonized. The WARMTH will continue to optimize harmonization in the practice of RAI therapy globally and promote utilization of multidisciplinary teams of a specialist in thyroid cancer evaluation and management. The WARMTH will also encourage development of national or regional programs with a team of multidisciplinary thyroid cancer specialists in resource-constrained countries to provide the patients with a high-quality care and optimal outcomes.

In selecting patients for RAI therapy, demonstration of iodine avidity and cancer spread using RAI scintigraphy represents the core principle of radiotheragnostic approach that should guide personalized management instead of relying on less of a direct evidence for disease risk, such as the size of the primary tumor. The WARMTH will harness global resources of its member specialists to facilitate the development of prospective evidence on theragnostic approach to patients with DTC, who in the future may be risk stratified by an integrative risk index modeling, which combines genomic alterations with conventional staging systems.

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